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THE INFLUENCE OF VAGOTROPIC AND SYMPATHICOTROPIC STIMULI ON THE SECRETION OF GASTRIC MUCIN AND ITS FRACTIONS IN MAN—*George B. Jerzy Glass, M. D. and Linn J. Boyd, M. D.* 355

A RESIN-GASTRIC MUCIN MIXTURE IN THE MEDICAL MANAGEMENT OF PEPTIC ULCER—*Frederick Steigmann, M. D. and Robert B. Schlesinger, M. D.* 361

EFFECT OF SHOCK UPON THE MORTALITY RATE OF PERFORATED PEPTIC ULCER—*Roland P. Reynolds, M. D., Meyer O. Cantor, M. D. and Charles Stebbins, M. D.* 365

THE EFFECTS OF VARIABLE INTERVALS OF COOLING UPON THE RESPONSES OF THE LAPIN INTESTINE AND UTERUS AND THE FELINE INTESTINE TO HISTAMINE, ACETYLCHOLINE, PITUITRIN AND BARIUM CHLORIDE—*Bradford N. Craver and Walter E. Barrett* 367

ACTIVITY OF CASHEW (ANACARDIUM OCCIDENTALE) NUTSHELL OIL IN HUMAN ANCYLOSTOMIASIS—*F. W. Eichbaum, D. Koch-Weser and A. T. Leao* 370

DIFFERENTIAL DIAGNOSIS OF OBSTRUCTIVE JAUNDICE—*George A. Wagner, M. D.* 371

DIVERTICULA OF THE STOMACH—*Gustave Rosenburg, M. D.* 373

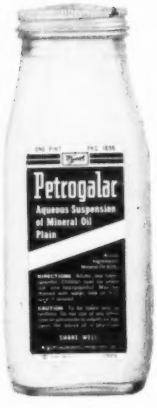
A POST-OPERATIVE ANALYSIS OF THE GASTRIC CHEMISTRY IN CASES FOLLOWING GASTROENTEROSTOMY AND PARTIAL GASTRECTOMY FOR DUODENAL ULCER—*Meyer Golob, M. D.* 377

ABSTRACTS ON NUTRITION, EDITORIAL, BOOK REVIEWS, GENERAL ABSTRACTS OF CURRENT LITERATURE 355-386

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HABIT TIME OF BOWEL MOVEMENT





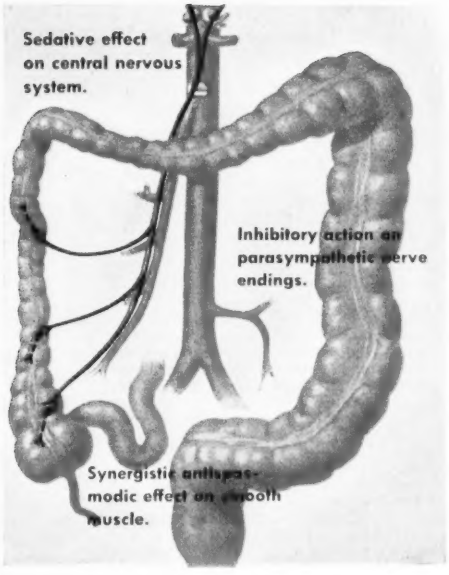
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1. Sollmann, T.: A Manual of Pharmacology. Philadelphia, W. B. Saunders Co., 7th ed., 1948, p. 938.
2. Batterman, R. C., and Ehrenfeld, I.: Gastroenterology, 9:141, Aug./ 1947.

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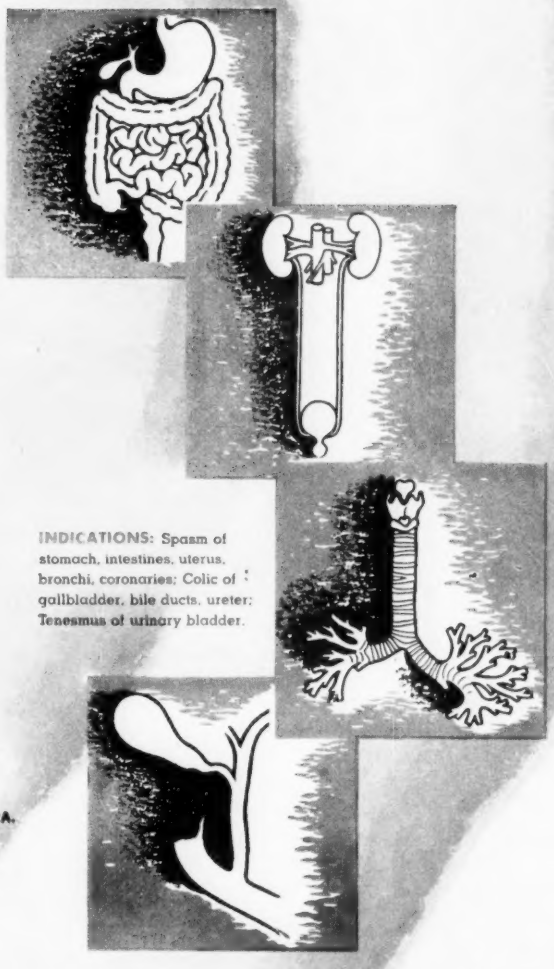
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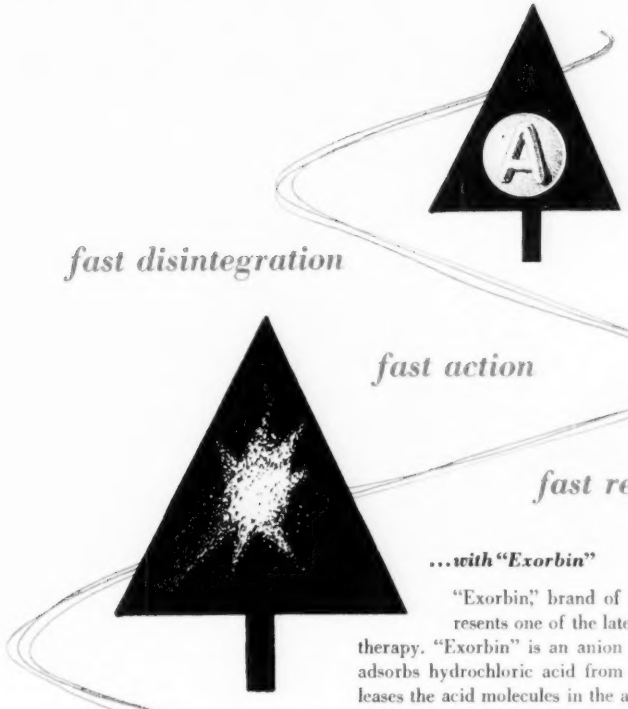
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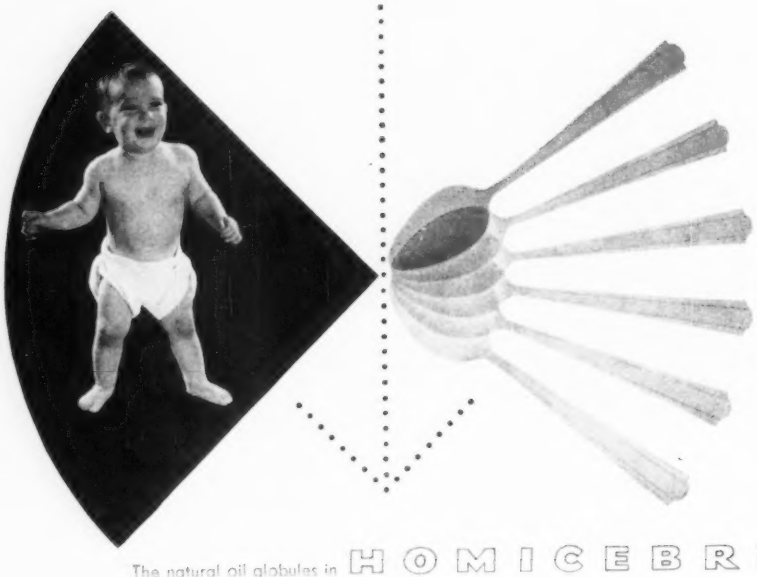
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THE INFLUENCE OF VAGOTROPIC AND SYMPATHICOTROPIC STIMULI ON THE SECRETION OF GASTRIC MUCIN AND ITS FRACTIONS IN MAN*

GEORGE B. JERZY GLASS, M.D. AND LINN J. BOYD, M.D. New York, N. Y.

THE effect of various vagotropic and sympathicotropic stimuli on gastric secretion has been studied extensively in man and animals by many investigators. In these studies central nervous stimulation as well as peripheral cholinergic and sympathicotropic stimulation were employed to collect data on the effect of these stimuli on the secretion of hydrochloric acid and pepsin(1-3).

Information on the effect of the same stimuli upon the secretion of gastric mucin is rather scanty and conflicting. While observations have been made on the effect of acetyl-choline(4), acetyl-beta-methylcholine(4-8), neostigmine(4, 5, 9), pilocarpine(10-18), insulin(7, 19), stimulation with an electrical current (20-23), sham feeding (24-27), epinephrine and ephedrine(9, 16) upon gastric mucin secretion in man and animals, in most instances the concentration of mucin was estimated only visually with and without centrifugation(5,9,10,11,14,15,16,18,20,21). In only a few of these studies was gastric mucin determined chemically by a turbidity test(19), by determining the reducing power of the gastric juice and mucin precipitate(7,15,17) or by colorimetric reactions based upon the polysaccharide content of mucin (26, 27).

Within the last few years additional knowledge was obtained on the heterogeneity of the gastric mucin complex(28-32) which was shown to have at least three components: 1) visible gastric mucus, i.e. the product of the surface columnar epithelial cells, 2) dissolved gastric mucoproteose, the dissolution and split product of surface epithelium mucus, and 3) dissolved gastric mucoprotein, a soluble product of the mucoid cells of the gastric glands. These substances differ from each other physically and chemically and in their origin, mechanism of secretion, physiological and clinical significance(33).

By means of a new method the effect of humoral and central nervous stimulation on these mucin fractions was studied. Contrary to data obtained with older methods(7,19), the inferences of Babkin and his collaborators concerning the vagal mechanism of mucin secretion(1,21-23) were confirmed and extended(32,33). It was shown that insulin represents a very powerful and reliable stimulus for the secretion of gastric mucin in man and especially for the secretion of dissolved gastric mucoprotein(33-35), i.e. the fraction secreted by the gastric glands.

The present paper deals with the effect of cholinergic and sympathicotropic drugs (neostigmine methylsulfate or Roche prostigmine, acetyl beta-methylcholine or mecholyl of Merck, pilocarpine and ephedrine) upe-

*From the Department of Pharmacology, The New York Medical College, Flower and Fifth Avenue Hospitals.
Submitted Jan. 27, 1950.

TABLE I. THE EFFECT OF PROSTIGMINE, MECHOLYL, PILOCARPINE AND EPHEDRINE ON THE VOLUME OF GASTRIC SECRETION AND ON ITS FREE AND TOTAL ACIDITY

	Volume of secretion in cc. per specimen					Free acid in mEq. per liter					Total acidity in mEq. per liter				
	Fast.	After stimulation 1	2	3	4	Fast.	After stimulation 1	2	3	4	Fast.	After stimulation 1	2	3	4
Prostigmine (0.5-1.0 mgm. subcutaneously)															
Means	15.7	17.3		15.1	12.2	29.0	31.6		34.3	43.9	40.3	46.7		50.9	55.4
Standard error	1.7	2.9		2.2	2.4	5.5	5.2		7.6	12.6	6.5	5.7		8.5	15.1
Number of tests	19	18		18	10	18	17		14	7	18	17		14	7
Mecholyl (15-20 mgm. subcutaneously)															
Means	17.8	24.8	18.1	15.6		14.1	20.2	28.4	17.4		26.9	33.3	41.8	32.2	
Standard error	3.9	5.5	3.3	3.0		4.5	7.8	8.8	7.1		6.2	8.0	9.8	8.8	
Number of tests	10	9	10	8		10	10	10	8		10	10	10	8	
Pilocarpine (15 mgm. orally)															
Means	20.8	18.2	15.5	20.4	11.5	26.4	18.2	20.7	23.4	36.2	40.4	20.5	35.7	37.2	34.5
Standard error	4.3	2.6	8.2	7.9	2.5	10.5	12.2	9.7	9.2	14.4	12.2	13.2	10.0	12.6	19.8
Number of tests	5	5	4	5	4	5	4	4	5	4	5	4	3	5	4
Ephedrine (50 mgm. orally)															
Means	16.6	18.0		17.7		12.9	25.0		25.7		27.7	43.6		42.7	
Standard error	2.9	5.9		5.5		6.9	6.2		9.8		9.7	8.2		12.6	
Number of tests	9	8		7		8	7		7		8	7		7	

F., average of two fasting specimens collected at intervals of 15-20 minutes.
Specimens 1 and 3 after prostigmine and ephedrine were collected 20 and 40 minutes after stimulation. Specimens 1, 2 and 3 after mecholyl and pilocarpine were collected 15, 30 and 45 minutes after stimulation. Specimen 4 after prostigmine, mecholyl, pilocarpine and ephedrine was collected 60 minutes after stimulation.

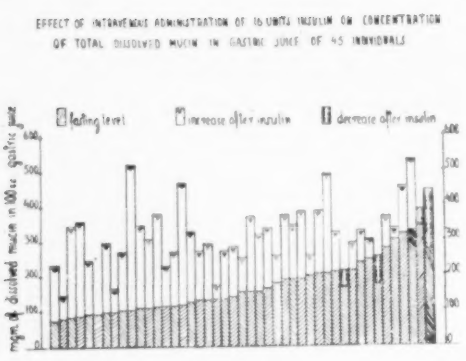


Figure 1.

on the secretion of gastric mucin and its fractions in man. This effect was compared to that of central nervous stimulation with insulin.

MATERIAL AND METHOD

The effect of peripheral vagotropic and sympathicotropic stimulation was studied on 30 individuals; 22 subjects were normal or had nervous indigestion, 5 duodenal ulcer, 1 atrophic gastritis, and 2 had had subtotal gastric resection for duodenal ulcer.

Fifty tests were performed on these individuals; 19 with prostigmine (0.5-1.0 mgm. subcutaneously), 10 with mecholyl (15-20 mgm. subcutaneously), 5 with pilocarpine (15 mgm., orally), 10 with ephedrine (50 mgm. orally) and 6 with insulin (16 U intravenously). As a background for the evaluation of the results of these tests 118 insulin tests were performed on 105 individuals including normal subjects as well as those with various functional and organic gastric disorders. These insulin tests have been reported and discussed elsewhere(33-35).

The tests were performed as follows: Two fasting contents were aspirated at intervals of 15-20 minutes; the stimulus was then administered and 3-4 specimens were withdrawn at intervals of 15-20 minutes during the hour after stimulation. By changing the position of the tube and patient, an attempt was made to collect each gastric specimen as completely as possible. The patient was carefully watched and cautioned to expectorate saliva and sputum into a basin to prevent dilution of the gastric content by these contaminants; this was particularly important after stimulation with pilocarpine and mecholyl.

In each specimen we determined the volume of fluid gastric juice after centrifugation, the free gastric acidity by titration to a salmon color with Toepfer's reagent and 0.05 N NaOH, the total gastric acidity using phenolphthalein as an indicator, and the dissolved gastric mucin and its fractions.

Total dissolved gastric mucin was determined by a colorimetric tyrosine method previously described(29) and its two fractions (dissolved mucoprotein and mucoproteose) by a previously reported fractionation technic(31) and method(32). When total dissolved mucin alone was determined without fractionation into its components, the volumetric tyrosine index of dissolved mucin was estimated by a procedure reported elsewhere(30).

This volumetric tyrosine index of dissolved mucin is the tyrosine content in mgm. in 1 cc. of dissolved mucin precipitate obtained by addition of 1½ volumes of acetone to the trichloracetic acid filtrate of gastric juice, incubated at 40°C for 1 hour and subsequently centrifuged for 5 minutes at 2000 RPM. This index is based on different hydration and therefore different volumes of both fractions of dissolved gastric mucin and indicates with some approximation the percentual relation of mucoprotein and mucoproteose in the mucin precipitate. The higher the index is, the more mucoproteose and the less mucoprotein is present; the lower the index is, the more mucoprotein and the less mucoproteose content of the dissolved mucin complex.

The results obtained were statistically evaluated and the means, standard deviations, standard errors, and the significance of changes by computing the value of "t" and "P" by routine methods (36, 37) were determined.

RESULTS

The results are listed in Tables 1-3 and their statistical evaluation in Table 4.

Prostigmine. Table 1 shows that prostigmine did not cause any definite change in the volume of gastric secretion or in gastric acidity. There was only a slight increase in volume of secretion 20 minutes after

TABLE 2. THE EFFECT OF PROSTIGMINE, MECHOLYL, PILOCARPINE AND EPHEDRINE ON THE CONCENTRATION OF THE TOTAL DISSOLVED MUCIN IN THE GASTRIC JUICE

	Total dissolved gastric mucin in mgm. per 100 cc. gastric juice					Volumetric tyrosine index of the dissolved gastric mucin				
	Fast.	After stimulation				Fast.	After stimulation			
		1	2	3	4		1	2	3	4
Prostigmine (0.5-1.0 mgm. subcutaneously)										
Means	207	243		223	257	2.7	2.1		2.4	2.5
Standard error	16	20		20	50	0.2	0.2		0.2	0.5
Number of tests	19	19		16	9	11	10		9	5
Mecholyl (15-20 mgm. subcutaneously)										
Means	244	365	295	266	248	2.6	2.1	2.2	2.3	2.1
Standard error	32	65	37	56	36	0.4	0.4	0.2	0.4	0.2
Number of tests	9	9	9	7	6	5	5	5	4	5
Pilocarpine (15 mgm. orally)										
Means	189	120	215	175	170	2.5	2.3	2.2	2.1	1.7
Standard error	37	25	79	58	54	0.2	0.2	0.2	0.2	0.1
Number of tests	5	5	3	5	4	5	5	4	5	5
Ephedrine (50 mgm. orally)										
Means	194	225		214		3.9	2.9		2.9	
Standard error	38	35		39		0.5	0.5		0.6	
Number of tests	10	9		8		6	6		5	

Specimens F., 1, 2, 3 and 4 as shown in Table 1.

stimulation in about one-half of the experiments and a slight increase in acidity 40-60 minutes after stimulation in a few of the cases studied. In general no statistically significant changes (Table 4) were noted.

In a majority of cases the total dissolved gastric mucin (Table 2) increased so that the average value rose 17.4 per cent 20 minutes and 24.1 per cent 60 minutes after the injection of prostigmine. The volumetric index (Table 2) showed a statistically significant decrease (Table 4) occurring 20-40 minutes after stimulation in a majority of cases. This indicates a shift in the composition of dissolved mucin in the direction of a predominance of mucoprotein and a relative decrease of the mucoproteose fraction.

This inference is confirmed by tests (Table 2) in which both fractions of mucin were studied simultaneously. In 5 of 7 instances an increase of mucoprotein and a decrease in mucoproteose was noted. Although the increase of mucoprotein averaged 36 per cent 20 minutes after the injection of prostigmine and the mucoproteose fell about 23 per cent there was, however, no statistically confirmed evidence of a constant and uniform shift within the mucin complex after prostigmine stimulation (Table 7). Moreover, the increase in total mucin concentration after prostigmine statistically was not significant.

Mecholyl. As shown by Table 1 mecholyl injected subcutaneously, in about one-half the cases caused a slight increase in the volume of gastric secretion and its free acidity, the average of the latter being doubled 30 minutes after the injection of mecholyl. These changes were, however, not remarkable except in one case and, statistically, were not significant for the value of "P" was only 0.1-0.2.

The dissolved mucin of the gastric juice showed (Table 2) an increase in 7 of 9 cases, the average level increasing 50 per cent 15 minutes after injection, i.e. at a time when most of the other signs of a mecholyl effect (sweating, sialorrhoea, bradycardia, redness of the face) appeared. This increase lasted for the next 15-20 minutes and sometimes was associated with a decrease in the volumetric tyrosine index, the average of which fell from 2.6 to 2.1, 15 minutes after mecholyl was injected.

The determination of mucoprotein and mucoproteose fractions 15-30 minutes after mecholyl (Table 3) showed an important increase in mucoprotein concentration in 3 of 4 cases; the mucoproteose concentration increased slightly in 3 and decreased in 2 other instances at the same interval.

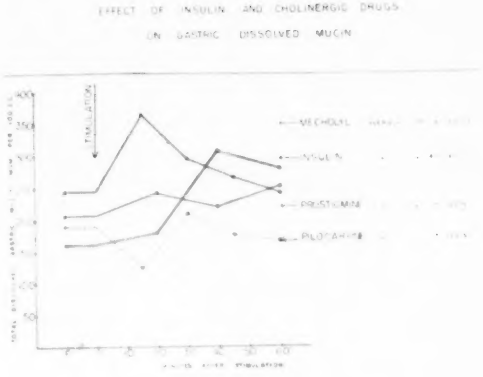


Figure 2.

The statistical evaluation of changes in gastric acidity, gastric mucin and its fractions after the injection of mecholyl (Table 4) indicates that the changes just described, though considerable in many cases, were not significant however, owing to their inconstancy and the variable extent of the response in different individuals.

Pilocarpine. It is evident from Tables 1 and 2 that pilocarpine, orally administered to man, did not appreciably increase the volume of gastric secretion, gastric acidity, nor the concentration of dissolved gastric mucin and its fractions except in one case of duodenal ulcer. Rather there is a tendency to lower values of gastric mucin 15 minutes after pilocarpine which, after 15 minutes, climbs back to its pre-stimulation level. None of these changes are statistically significant (Table 4).

The only constant feature of pilocarpine stimulation was the decrease in the volumetric tyrosine index of dissolved mucin which occurred 15-45 minutes after the ingestion of pilocarpine and fell to its nadir in about 1 hour. This decrease in the volumetric tyrosine index statistically was highly significant and indicated a relative shift within the gastric mucin complex in favor of the mucoprotein component.

Ephedrine. The data listed in Tables 1 and 2 indicate in some of the cases examined after the ingestion of ephedrine, a slight increase in the volume

TABLE 3. THE EFFECT OF PROSTIGMINE AND MECHOLYL ON THE CONCENTRATION OF THE DISSOLVED MUCOPROTEIN AND MUCOPROTEOSE IN THE GASTRIC JUICE

	Dissolved mucoprotein in mgm./100 cc. gastric juice				Dissolved mucoproteose in mgm./100 cc. gastric juice			
	Fast.	After stimulation 1	2	3	4	Fast.	After stimulation 1	2	3	4
	Prostigmine (0.5-1.0 mgm. subcutaneously)									
Means	42	57		49	51	183	130		126	85
Standard error	12	15		14	17	43	28		28	25
Number of tests	7	7		6	5	7	7		7	3
	Mecholyl (15-20 mgm. subcutaneously)									
Means	38	125	120	75		339	253	191	112	
Standard error	9	68	42	31		81	54	25	32	
Number of tests	4	4	4	4		5	5	5	4	

of gastric secretion and acidity as well as an increase in the dissolved gastric mucin concentration in about one-half of them. Usually this happened about 20-40 minutes after stimulation but statistical evaluation (Table 4) shows this was not significant. These changes were associated in most instances with a decrease in the volumetric tyrosine index of gastric mucin. This was observed in 5 out of 6 cases examined, 20-40 minutes after the ingestion of ephedrine.

COMPARATIVE EFFECT OF CHOLINERGIC DRUGS AND INSULIN UPON GASTRIC MUCIN

It was shown in previous studies that 1/6 U. of insulin administered intravenously represents a very powerful and constant stimulus for the secretion of gastric mucin in man, providing the vagi and the gastric mucosa are intact(32-35). This effect is due to the stimulative effect of hypoglycemia upon the vagal centers; the stimulus is transmitted to the stomach through the vagi and seems to act directly upon the mucin producing cells(38). The effect of insulin upon mucin secretion is very uniform, as shown by Figure 1, which lists some of our previous results.

Figure 2 compares the effect of insulin with that of cholinergic drugs upon the concentration of dissolved mucin in human gastric juice. Each curve represents the average of many tests.

It is evident from this graph that insulin, mecholyl, and, to a lesser extent prostigmine, on the average, increase the concentration of dissolved mucin in human gastric juice. The effect of mecholyl is exerted immediately after the injection (first 15 minutes), that of prostigmine occurs somewhat later, while the peak of the insulin effect is simultaneous with the signs of hypoglycemia, usually about 40 minutes after the injection.

Statistical evaluation of the effect of cholinergic drugs and insulin upon gastric mucin and its fractions as well as on gastric acidity (Table 4) indicates that the stimulative effect of insulin is much more significant than that exerted by cholinergic substances. This is shown by values of "P" which are highly significant (below 0.001) in respect to insulin and much less significant (0.1-0.2) for cholinergic drugs. Despite the fact that mecholyl or prostigmine in many instances exert a definite stimulative action upon gastric mucin (Fig. 2), nevertheless their effect is insignificant statistically in comparison to that of insulin.

This is also evident from Table 5 which compares the effects of insulin with those of cholinergic drugs as tested in the same individuals. This was done with mecholyl in 2 subjects, with prostigmine in 4 and with pilocarpine in 4.

Fractionation studies show that the effect of insulin upon gastric mucin is very uniform and powerful, particularly with respect to the fraction secreted by the mucoid cells of the gastric glands, i. e. gastric mucoprotein. This stimulating effect of insulin manifests itself in its action upon gastric pepsin (7,39) and hydrochloric acid secretion (1) and consequently holds for all secretory elements of gastric glands. Its effect

TABLE 4. STATISTICAL EVALUATION OF THE EFFECTS OF CHOLINERGIC AND SYMPATHICOTROPIC DRUGS AS COMPARED TO THAT OF INSULIN ON THE GASTRIC ACIDITY, GASTRIC MUCIN AND ITS FRACTIONS.

Stimulus	Gastric component examined	Time interval after stimulation in minutes	Difference of the means (D) between fasting value and after stimulation	Standard error of the difference of the means (ED)	"t" (D/ED)	"n"	Probability of significance ("P") at corresponding "t" and "n"
Prostigmine (0.5-1.0 mgm. subcut.)	Free HCl	60	+14.9	13.7	1.09	19	0.3
	Total dissolved mucin	20	+36.0	25.8	1.39	19	0.2-0.1
	Volumetric tyr. index	20	−0.6	0.22	2.72	12	0.02-0.01
	Diss. mucoprotein	20	+15.0	19.2	0.78	7	0.5-0.4
	Diss. muceprotease	40	−59.0	51.0	1.16	7	0.3-0.2
Mecholyl (15-20 mgm. subcut.)	Free HCl	30	+14.3	9.9	1.44	10	0.2-0.1
	Total dissolved mucin	15	+121.0	72.6	1.67	9	0.2-0.1
	Volumetric tyr. index	30	−0.40	0.44	0.91	5	0.4
	Diss. mucoprotein	30	+82.0	42.9	1.91	4	0.2-0.1
	Diss. muceprotease	30	−118.0	84.8	1.75	5	0.2-0.1
Pilocarpine (15 mgm. orally)	Free HCl	60	+9.8	17.8	0.55	5	0.6
	Total dissolved mucin	15	+69.0	44.6	1.55	5	0.2-0.1
		30	+24.0	87.2	0.28	5	0.8
	Volumetric tyr. index	60	−0.8	0.22	3.64	5	0.02-0.01
Ephedrine (50 mgm. orally)	Free HCl	20	+12.1	9.3	1.30	8	0.3-0.2
	Total dissolved mucin	20	+29.0	51.8	0.56	9	0.6
	Volumetric tyr. index	20	−1.0	0.70	1.43	6	0.2
Insulin (1/6 U. intravenously)	Free HCl	60	+51.0	9.1	5.60	12	below 0.001
	Total dissolved mucin	40	+115.0	28.0	4.11	45	below 0.001
	Diss. mucoprotein	40	+128.0	9.7	13.20	12	below 0.001

upon the columnar cells of the surface epithelium and its products: visible mucus and dissolved gastric mucoproteose, is much less evident (32,33).

The same is true of the cholinergic drugs in respect of gastric mucoprotein. Tables 2 and 4 show that all cholinergic substances tested decreased the volumetric tyrosine index of dissolved mucin and that this change was statistically significant in respect to pilocarpine and prostigmine. This means a shift in the composition of mucin in favor of mucoprotein and a decrease of the mucoproteose fraction. The effect of cholinergic drugs was, however, more indefinite and less uniform than that exerted by insulin. The superiority of insulin over prostigmine is evidenced by the curves drawn in Fig. 3 which presents the average value of the mucin fractions after prostigmine and insulin stimulation in the same individuals when one test is run after the other.

The superiority of insulin as a uniform stimulus for mucoprotein secretion is also evidenced by data drawn in Fig. 4 which compares the effect of insulin, mecholyl, and prostigmine stimulation in 23 normal subjects. The variability of the response of mucoprotein after prostigmine or mecholyl is contrasted with the uniformity of response to insulin.

AVERAGE CURVES OF MUCOPROTEIN AND FREE ACIDITY OF THE GASTRIC JUICE AFTER PROSTIGMINE – INSULIN INJECTION
(MEANS OF 3 TESTS CALCULATED WITH STANDARD ERROR

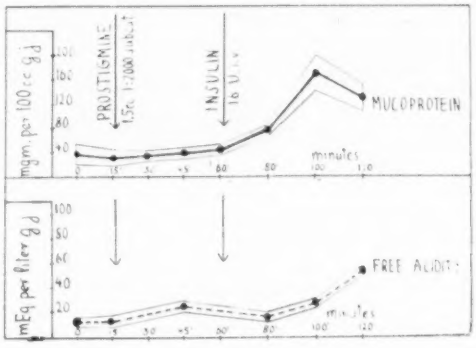


Figure 3.

COMMENT

A general feature of the action of cholinergic drugs upon gastric secretion and more specifically upon gastric mucin and its fractions is its variability and inconsistency. Although very effective in one individual they are devoid of any effect in another although administered in the same dose and to people without any organic lesion of the gastric mucosa. Since the effect of these substances is almost exclusively peripheral, it must be postulated that these differences in response depend upon varying irritability of peripheral organs, i. e. the gastric mucosal cells and peripheral nerve endings or ganglia. The same factor has been considered responsible for a more or less strong response of some individuals to central vagal stimulation (30).

Differences in response have been noted by various authors in respect to this group of substances (1,6,8). For instance, it is known that not only dosage (1,6,8,15) but also the species of the experimental subject is decisive for the response as shown by the positive response of the dog to pilocarpine (14) but no response in cats (15), or by a strong effect of mecholyl upon gastric secretion in dogs (6), but less consistent in man as indicated by our studies and a negative response in mice (39).

This feature explains the discrepancy of results among many previous workers in regard to the action of cholinergic substances upon gastric secretion; this is exemplified by the conflicting results of some writers concerning the action of mecholyl (40, 41) or pilocarpine (3,7,12,13,16,18) on gastric secretion. Our data agree in general with the observations of Wolf and Wolff (9) concerning the effect of prostigmine and ephedrine upon the secretion of gastric mucin and that of mecholyl upon gastric acidity as well as with the observations of Hollander (3, 18) concerning the lack of effect of pilocarpine upon the secretion of gastric mucin. The stimulating effect of ephedrine upon gastric mucin in some of our tests may parallel the augmented secretion of gastric mucin following irritation of the sympathetic nerves reported in animals by Baxter (15).

Owing to the variability and inconsistency of individual response to cholinergic drugs—and this seems to hold also for peripheral sympathicotropic agents like ephedrine—these substances are entirely inadequate as gastric secretory stimuli. This is true in respect to the stimulation of gastric hydrochloric acid as well as of gastric mucin and its fractions. Insulin is, by far, superior as a comprehensive stimulus for gastric secretion (38).

TABLE 5. COMPARISON OF THE EFFECT ON TOTAL DISSOLVED MUCIN CONTENT OF THE HUMAN STOMACH OF THE INTRAVENOUS ADMINISTRATION OF 16 U OF INSULIN SUBCUTANEOUS INJECTION OF 1 CC., 1:2000 PROSTIGMINE OR 20 MGM. MECHOLYL, AND ORAL INGESTION OF 0.015 GM. OF PILOCARPINE IN THE SAME INDIVIDUALS

Total dissolved mucin in mgm. per 100 cc. of gastric juice.

Case	Insulin test				Prostigmine test				Mecholyl test				Pilocarpine test			
		After insulin				After prostigmine				After mecholyl				After pilocarpine		
	F.	20'	40'	60'	F.	20'	40'	60'	F.	15'	45'	60'	F.	15'	45'	60'
3	194	207	349	224	160	150	194	156					290	164	134	207
9	194	168	387	249	140	330	266	283	190	722	429	349	200	112	381	266
2	126	316	328	193	162	286	247	187								
4	209	191	393	170									205	187	204	188
6	166	197	344	252	163	184	146		243	216	180					
5	82	135	364										63	40	43	20

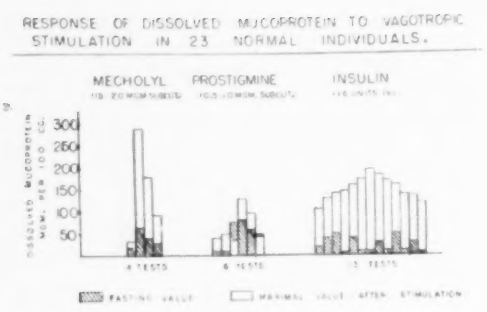


Figure 4.

SUMMARY AND CONCLUSIONS

The effect of cholinergic substances (prostigmine, mecholyl, and pilocarpine) and sympathicotropic substances (ephedrine) was studied in respect to their action upon gastric mucin, its fractions, gastric acidity and volume of gastric secretion in man. This effect was compared to that of the central stimulating vagotropic action of insulin administered intravenously.

Prostigmine, 0.5-1.0 mgm. subcutaneously, in 19 individuals did not appreciably affect the volume and acidity of gastric secretion but caused in most instances, 20-40 minutes after injection, an increase in dissolved gastric mucin. This increase concerned for the most part dissolved gastric mucoprotein, the origin of which has been traced to the mucoid cells of the gastric glands.

Mecholyl, 15-20 mgm. subcutaneously, in 10 individuals increased the volume and acidity of gastric secretion in about one-half the individuals tested and it also frequently increased the concentration of dissolved mucin in the gastric juice. The rise was due mainly to an increase of the mucoprotein fraction.

Pilocarpine, 15 mgm. orally, in 5 individuals had no appreciable stimulating effect upon the volume and acidity of gastric secretion nor upon total dissolved mucin of the gastric juice, the concentration of which actually showed a tendency to decline. In this instance as well, the mucoprotein fraction in the mucin complex tended to increase after pilocarpine was administered.

Ephedrine, 50 mgm. orally, in 10 subjects showed a slight stimulative effect upon the volume and acidity of gastric secretion as well as upon the concentration of dissolved gastric mucin in about one-half the tests. In most instances a tendency of the mucoprotein fraction to prevail in the gastric mucin complex after stimulation by ephedrine was noted.

The action of cholinergic drugs upon gastric secretion and more specifically upon the secretion of gastric mucin and its fractions is, however, variable, inconstant and dependent not only upon the dosage, the presence or absence of mucosal lesions but also upon individual variability or irritability of peripheral organs. Statistical evaluation of the results obtained indicates a statistical insignificance of most of the changes noted, a result of a varying response of different individuals to peripheral stimuli. This precludes the employment of cholinergic substances as vagal secretory stimuli in man for the routine study of the nervous phase of gastric secretion.

In this respect cholinergic peripheral vagotropic stimuli compare unfavorably with centrally acting vagal stimuli as represented by insulin. The gastric secretory response to insulin, administered intravenously, has been tested 124 times in 111 individuals (normal subjects and those with different forms of gastric pathology) and found to be very uniform, marked, constant and statistically significant providing the vagi and the secretory cellular mucosal elements are intact. As shown by previous studies the stimulative effect of insulin upon gastric secretion is the most comprehensive and affects all the secretory components of the gastric glands (hydrochloric acid, pepsin, and gastric mucoprotein).

Quantitative interpretation of the data supports the thesis that central vagal stimuli (insulin) are more potent and uniform stimulators of gastric secretion than peripheral stimuli in the form of cholinergic or sympathicotropic drugs.

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A RESIN-GASTRIC MUCIN MIXTURE IN THE MEDICAL MANAGEMENT OF PEPTIC ULCER

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ADAMS AND HOLMES (1) in 1935 first described the use of synthetic resins as exchange adsorbents. However, not until 10 years later was this property of resins studied biologically when Segal (2) and his associates noted that a polyamine formaldehyde resin (Amberlite IR-4) would promptly adsorb acid from gastric secretion of rats. Shortly thereafter Martin and Wilkinson (3) demonstrated that the decreasing particle size or mesh size of the resin increased the speed of acid removal and that resin inhibited peptic activity. These workers concluded that resins as antacids closely approximate the ideal of an insoluble, nonirritant substance which, while neutralizing acid, has no effect on the acid-base equilibrium of the body, does not alkalinize the urinary tract, does not cause diarrhea or constipation and has no serious effect on the mineral balance by virtue of its nonremoval of phosphates and/or chlorides. They also found resins nontoxic to animals in long time feeding experiments, a fact which was also noted by others (4).

The above reports led to a more extensive application of resins to clinical medicine, particularly to peptic ulcer therapy. Thus Spears and Pfeiffer (5) tested the effect of resins on ulcer in a group of 30 ulcer patients and others with abdominal symptoms and reported very good results. Kraemer and Lehman, Jr. (6) noted some excellent results in a small number of intractable peptic ulcer cases, whom they treated with the new resin preparation. Later Kraemer and Siegel (7) reported on a larger series of cases whom they treated for one to 10 months with just as effective results as with the usually employed metallic salt antacids but without some of the untoward results

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of the latter. They noted no evidence of toxicity from 2 to 9 gm. of the drug taken daily for six to eight months; skin, blood and urine were not affected, nor was the gastric mucosa as checked in some patients by gastroscopy and in three by examination of the resected stomach. Weiss (8) and Marks (9) have also reported good symptomatic results with anion exchange resin in patients with gastroduodenal ulcers. The former was able to show x-ray regression of the ulcer crater in within 10 to 14 days in about 90 per cent of his patients. Wirts and his associates (10) found anion exchange resin effective in neutralizing acid and inactivating pepsin in the gastric juice without causing rebound in gastric acidity or affecting the gastric emptying time.

In the past five years we have, in our clinic, investigated the antacid effects of many substances, some of which were then given a clinical trial on a variable number of patients with gastroduodenal ulcers. Hence when the reports of the new type of "antacid" appeared we planned to investigate it as an additional substance. Accordingly the antacid effect of various resinous substances was tested on a number of patients with gastroduodenal ulcer. One of these substances was also tested clinically for its therapeutic effect in patients with peptic ulcer.

PROCEDURE AND MATERIAL

As in other similar studies the following procedure was followed: Fasting patients were intubated with a Levine tube and their gastric contents were completely aspirated. The aspiration was repeated at 15 minute intervals until 4 samples were obtained. After the fourth sample was obtained, the patient was given 0.7 cc. of histamine phosphate (0.1 mg. for 10 Kg. weight) and the aspirations were continued every 15 minutes for another 90 minutes. The free and total acidity of each sample was determined and plotted as a graph. On successive days the patient received the antacid to be tested—in this case one of the resin preparations simultaneously with the histamine injection. Aspirations were continued as on the previous day. The difference in the height of the curves following histamine alone and histamine plus antacid was taken as the measure of antacid effect. The following resins were used and in variable doses: (1) Polyamine methylene resin (Resinat), (2) Polyamine methylene resin with mucin, (3) De-Acidite (Amberlite IR-4), and (4) Polyamine anion exchange resin with mucin (Resmicon).*

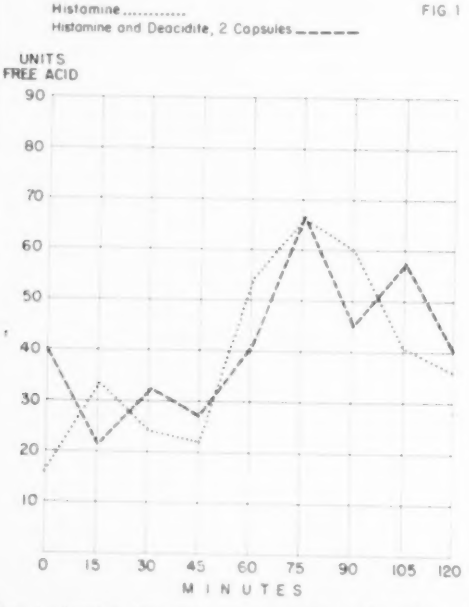


FIG. 1

Fig. 1—Average free acid curves comparing the effect of histamine stimulation without and with the antacid.

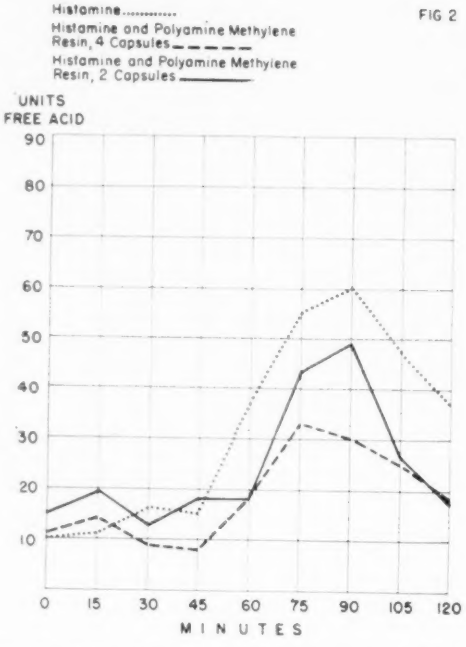


FIG 2

Fig. 2—Average free acid curves comparing the effect of histamine stimulation without and with 2 and 4 capsules of the antacid respectively.

A group of 30 patients—some of whom had undergone the antacid tests previously were observed for the clinical effect of "Resmicon" over a period of 2 to 15 months. The results were graded according to the immediate symptomatic relief, the length of the asymptomatic period, the number of recurrences of symptoms and the general clinical course. The patients with gastric ulcer had repeated X rays to note the decrease in size of the crater. Some patients with gastric ulcer were repeatedly gastroscoped in order to check the healing gastroscopically and also to note the degree of coating effect, if any.

Ninety observations were done for the antacid study. In 18 patients the antacid effect of 4 capsules of Polyamine methylene resin was tested, that of 2 capsules in 21 patients. In 20 patients the antacid effect of De-Acidite was tested. The acid inhibition of 2 tablets of Polyamine anion exchange resin with mucin was tested in 15 patients and of 4 tablets in 16 patients.

Thirty patients were given 2 tablets of Polyamine anion exchange resin with mucin (Resmicon) every 2 hours for 6 to 8 doses daily for the first week on treatment. Then according to the results the dose was continued at the same level or decreased. Usually the dose was decreased to 2 tablets after meals and at bedtime and thus continued for several months while under observation. Most of the

*Supplied to us by the Whittier Laboratories, Chicago, Ill.

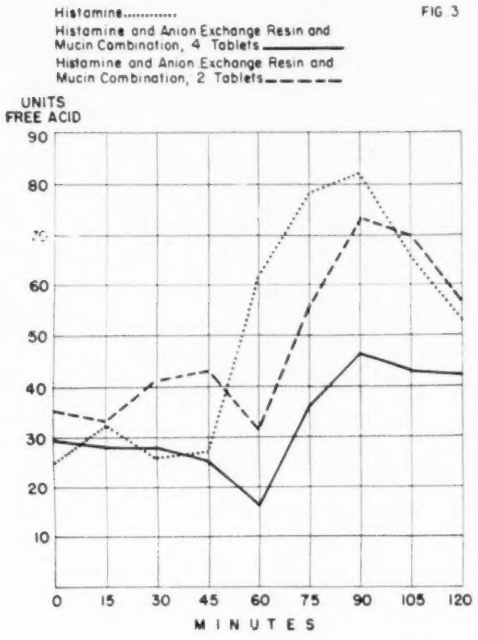


FIG 3

Fig. 3—Average free acid curves comparing the effect of histamine stimulation without and with 2 and 4 tablets of the antacid respectively.

patients chosen were those who did not respond well to therapy with other antacids. All patients were put on a bland diet and received antispasmodics and sedatives in addition.

Of the thirty patients treated with this new resin-mucin mixture 23 were men and 7 females. Twenty-three had a duodenal ulcer, 5 a gastric ulcer, one had a gastric and a duodenal and one a marginal ulcer. Four were colored and 26 white. Most of them had an ulcer history of several years duration and had been previously on various ulcer regimes.

RESULTS

Antacid Study

The results of the study of the antacid effect are shown graphically in Figures 1, 2, 3 and 4. It will be noted that the coarse resin (Fig. 1) did not cause any appreciable decrease in acidity like the finer mesh (Fig. 2), as was pointed out by others (3). It is also evident that the admixture of gastric mucin enhances the antacid effect of the resins (Fig. 3), a fact which we previously demonstrated (11). From comparison with the antacid effect of other substances tested within the same period on some of these patients, it can be said the resin-mucin graphs compare favorably with those of other antacids presently used (Graph 4).

Clinical Study (Table I)

Most patients had good symptomatic relief within the first week (two to seven days) of "Resmicon" treatment. Several had to continue the large dose (12 to 16 tablets) for another week. They felt better, ate better and gained weight. The majority took the tablets well and there were no complaints regarding constipation or diarrhea. Some of the patients (20) have remained asymptomatic during the period of observation, six to 15 months, both on or without continuous treatment. Three patients had recurrence of symptoms five, seven and eight months respectively after stopping the treatment. These were promptly relieved by a new course of therapy. Two patients objected to the taste of the tablets, and two were uncooperative and therefore had to be dropped from the series after a period of observation. Three patients had occasionally mild symptoms of short duration so that they were elicited only by persistent questioning of the patient. These symptoms would usually occur after some dietary indiscretion or emotional upset.

Simultaneously with clinical improvement the patients with gastric ulcer showed significant changes in the size of the craters when x-rays were taken at weekly or bi-monthly intervals. Those who were gastroscoped (a total of 19) also showed healing of the ulcer. If "Resmicon" was given 45 minutes to one hour before gastroscopy, a coating effect on the ulcer was not always discernible. At times the crater was clean (not coated), at times filmy and at times the mucus appeared glary. In one case only a suggestive coating of the ulcer was noted and this patient had much gastric residue despite aspiration prior to gastroscopy.

COMMENT

Anion exchange resins have thus far found but little application in medicine. It is only in recent years

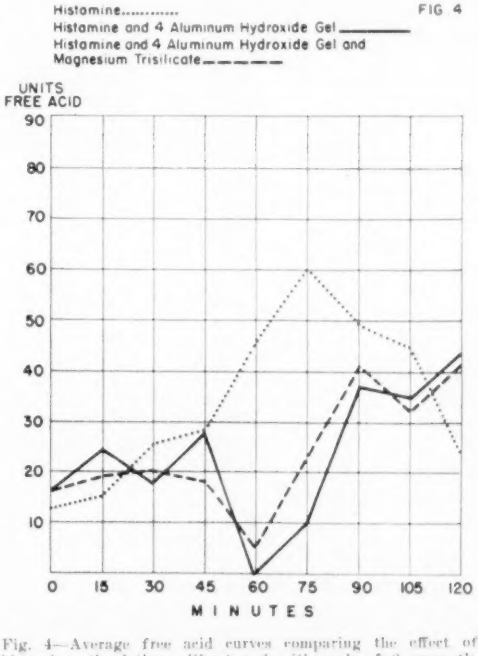


FIG 4

Fig. 4—Average free acid curves comparing the effect of histamine stimulation without and with each of 2 presently used antacids.

No.	Name, Age, Sex, Race	Diagnosis	Duration of Symptoms	Previous Treatment	Duration of Present Medication	Result	Remarks
1.	G.B., 54, F, B	G.U.	Months	Several types	6 months	Subjectively improved	Ulcer seen gastroscopically
2.	E.S., 40, F, B	G.U.	Months	Several types	2 months	Marked improvement	Ulcer healed by x-ray and gastroscopy
3.	A.H., 50, M, W	D.U.	Years intermittently	Several types	6 weeks	Little improvement	Discontinued--poor cooperation on part of Pt.
4.	S.B., 49, F, B	D.U.&G.U.	20 yrs. intermittently	Several types	14 months intermittently	Improved	No severe bouts of epigs. distress during this period, although pt. takes medication only intermittently.
5.	A.S., 30, F, B	D.U.	5 years	Slight	3 months	Very good	X-ray shows healing. Had only 1 mild bout of epig. distress as compared to frequent ones before
6.	A.H., 28, M, W	G.U.	Months	None--took occ. soda	5 months	Very good	Subjectively and objectively.
7.	A.S., 45, M, W	D.U. with mild obstruction	Years	Several types	2 months intermitt.	Improved	Uncooperative pt. takes medic. intermittently.
8.	L.L., 62, M, W	Vaginal ulcer	D.U.-18 yrs; V.U.-3 yrs.	Several types	13 months	Very good	Ulcer healed on x-ray
9.	A.O'B., 60, M, W	D.U.	Years	Several types	6 months	Improved	
10.	S.W., 40, M, W	D.U. with bleeding	6 Months	None--occ. soda	5 months	Improved	Headdual weakness
11.	L.S., 50, M, W	D.U. and arthritis	Years	Several	6 months	Improved	
12.	S.S., 64, M, W	G.U. with prev. perforation	Years	Several	6 months	Improved	Ulcer healed on x-ray
13.	L.F., 56, F, W	D.U.	Years	Several	13 months intermitt.	Improved	Takes medication intermittently--gets relief from medication
14.	W.W., 66, M, W	G.U. - colitis	Years	Several	2 months	Improved	Ulcer healed on x-ray
15.	E.C., 61, F, W	G.U.	2 years	Several	6 months	Very good	Ulcer healed on x-ray
16.	L.B., 56, M, W	D.U.	Years	Several	8 months	Very good	Pt. believes this medication checked his pain better than any other.
17.	A.S., 32, M, W	D.U.	2y years	Several types	14 months intermitt.	Very good	Took medic. for 6 mos. and felt very good; then stopped treatment and had recurrence 2 mos. later. Better now on medication.
18.	J.A., 50, M, W	D.U.	1 year	Amphojel & Belladonna	7 months	Improved	Subjective improvement
19.	W.G., 56, M, W	D.U.	Years	Several	13 months intermitt.	Improved	Good results--stopped medic. after 4 mos.; had recurrence 6 mos. later. Again relieved by medic.
20.	W.B., 69, M, W	D.U.	Years	Several	13 months	Improved	Ulcer crater healed on x-ray
21.	F.E., 56, M, W	D.U. and bleeding	Years	Several	13 months	Improved	No symptoms since on treatment
22.	I.M., 39, F, B	D.U. and duodenitis	Years	Several	13 months	Improved	No symptoms since on treatment
23.	G.F., 28, M, W	D.U.	2 years	Several	7 months	Very good	Pt. had good resp. Stopped medic. Felt O.K. when last seen 8 mos. ago.
24.	S.P., 32, M, W	D.U. and post-cholecystectomy	Years	Several	15 months intermitt.	Improved	Pt. improved while on medic. Had recurrence of symptoms 5 mos. after stopping it.
25.	A.S., 37, M, C	D.U. and bleeding	Years	Several	2 months	Improved	Did not like taste of tabs.
26.	J.C., 44, M, W	D.U.	Years	Several	11 months	Improved	No recurrence
27.	L.K., 52, M, W	D.U.	Years	Several	4 months	Improved	
28.	C.C.W., 34, M, C	D.U.	Years	Several	2 months	Improved	Taste objectionable. Stopped medic. as soon as symptoms free
29.	G.J., 70, M, C	D.U. with pyloric obstruc.	Years	Several	10 months	Improved	No recurrence
30.	L.M., 30, F, C	D.U.	Years	Several	6 months	Improved	No recurrence--slight constipation

Table I. Clinical resume and therapeutic results in 30 cases with gastroduodenal ulcer treated with a polyamine anion exchange resin with gastric mucin mixture (Resinous).

that use has been made of the valuable characteristics of these substances in removing ions from body fluids. It appears likely that resins with extreme selectivity will be developed which will be used for absorption for various toxic or disturbing chemicals in the intestinal tract and elsewhere.

The most important application of resins to date has been their use for the neutralization of the hydrochloric acid in gastric juice, without interfering with the acid-base balance. Several clinical studies have demonstrated their efficacy for this purpose (2, 5, 6, 7, 8). The recent introduction of a mixture of resin plus gastric mucin (Resmicon) has given the clinician a new resinous substance which promises to be superior to the plain resins, if observation on a small group of cases for a moderate length of time can be taken as a criterion. This new substance appears to combine the good effects of resins with those of gastric mucin in the treatment of gastroduodenal ulcer.

SUMMARY

Thirty patients with gastroduodenal ulcer were observed for periods of five to 15 months while on a regimen in which a new Polyamine anion exchange resin-gastric mucin mixture (Resmicon) was used as the antacid. Except for two patients who did not like the taste, all patients took this substance (12 to 16 tablets daily) without any untoward results.

Subjective improvement occurred quite promptly within the first week in the majority of cases. Objective improvement (by x-ray and gastroscopy) was noted within two to four weeks on most of those checked.

During the observation period — four patients were dropped from the study. Of the remainder only three had mild recurrence of symptoms during a period of observation of 12, 13 and 15 months respectively.

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EFFECT OF SHOCK UPON THE MORTALITY RATE OF PERFORATED PEPTIC ULCER

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THERE IS UNIVERSAL acceptance among surgeons everywhere that patients in shock should not be subjected to surgical intervention. We speak glibly of the patient being or not being in shock under the assumption that this state is so well defined that anyone can recognize its presence. While this holds true for the extreme type of case admitted to the hospital with a cold clammy skin, rapid pulse, blood pressure ranging below 80 mm. of mercury (systolic), and the appearance of impending death, it does not hold true for milder, but none-the-less important, types of shock in which the clinical picture is not too well defined.

The importance of this differentiation lies in the influence upon the surgeon's decision to intervene when confronted by an acute surgical emergency such as a perforated peptic ulcer. Very few surgeons would undertake to open the abdomen to close a perforation in the face of a picture of extreme shock. Many surgeons, however, overlook the milder states of shock, considering the acute surgical emergency, i.e., perforated peptic ulcer, as demanding immediate attention despite any other problem. In reviewing our statistics over the past six years ample evidence was unmistakably found that such surgical intervention may be disastrous for the patient unless even the milder shock states were first corrected.

For the purposes of this study we divided all patients admitted with a diagnosis of perforated peptic ulcer into two main groups: (1) those presenting clinical evidence of true shock as shown by cold clammy skin, blood pressure below 80 mm. mercury systolic, and a rapid pulse and (2) those presenting evidences of milder shock as characterized by blood pressure ranging between 80 to 100 mm. of mercury, subnormal temperature with a normal pulse and respiratory rate. We believe that the subnormal temperature is of great diagnostic significance in the diagnosis of patients in this group.

When studied from this point of view, we were able to review 143 patients admitted to Grace Hospital with a diagnosis of perforated peptic ulcer. The aver-

The Grace Hospital, Detroit.

age time that elapsed between the onset of perforation and the admission to the hospital was 7.3 hours. One patient, however, perforated while in the hospital for cholecystographic study. Immediately upon admission all such patients were examined by the surgical resident on duty and the physical status of the patient noted. Those patients in evident shock were so noted while those patients which did not present the typical findings of the shock syndrome were merely diagnosed as having a perforated peptic ulcer.

Of the 143 patients admitted with a diagnosis of perforated peptic ulcer, only 14 or 10 per cent of the total were diagnosed as being in true shock upon admission. This is quite understandable when it is considered that seven hours usually elapsed between the time of perforation and the admission to the hospital. In this period of time, many such patients would react from the shock state so that when admitted the true clinical picture of shock would be absent. The subnormal temperature, however, which is characteristic of the shock state, responds much slower. As a result many such patients upon admission to the hospital present only a subnormal temperature as the last remaining finding of the patient having been in shock.

For this reason, we reviewed the temperatures of all patients admitted with a diagnosis of perforated peptic ulcer in an effort to pick up all such cases. In so doing, 98 patients were found to have a subnormal temperature. This is an incidence of 70 per cent of all such admissions. We noted also that a failure to classify such patients as still being in the shock state and subjecting them to immediate surgery without preparation resulted in a much higher mortality rate than in the group in which adequate preparation had been instituted.

In reviewing the causes of death in this group of patients with perforated peptic ulcer, we noted that the mortality rate from shock accounted for 50 per cent of all deaths whereas peritonitis was responsible for only 40 per cent of the deaths. It is thus evident that the danger from shock is greater than the danger of death from peritonitis. Such being the case it would seem better surgery to allow adequate time for proper preparation of the patient following admission to the hospital instead of rushing the patient to the operating room to close the perforation. It would seem that the perforation could safely be permitted to wait until the state of reaction from the perforation had set in.

Three fairly well defined stages can be demonstrated in any patient subjected to a perforated peptic ulcer. Associated with the onset of the perforation is the stage of shock. This varies depending upon the size of the perforation and the condition of the patient. The larger the perforation the greater in general is the shock whereas pin-point perforations which develop slowly may present no clinical evidence of shock. Patients with this latter type of perforation are most difficult to diagnose as abnormal physical findings are usually meager. Patients vary greatly in their ability to withstand pain. Some are able to tolerate considerable pain with fortitude and calmness whereas other types appear to be extremely sensitive to pain. Such patients not infrequently faint as the first evidence of even mild shock with the slightest degree of pain. Between these two extremes are varying gradations of ability to withstand pain. One's ability to withstand pain is partially associated with the degree of shock found. Often the physical findings are found to be out of proportion to the pathology found especially in the high strung nervous type of individual. On the other hand, stolid individuals often present few evidences of shock aside from a subnormal temperature and at operation a fairly large perforation is often found. It would, therefore, seem wise to attempt to correlate the pain threshold of the patient with the physical findings before deciding upon the time of surgery.

The second stage following the shock which accompanies the perforation is the stage of reaction. This is the time during which all signs of shock disappear and the patient appears much improved. The blood pressure rises, the cold clammy skin changes to a warm moist skin, and the pulse becomes slower and steady. This is the optimum time for surgical intervention. Patients operated upon during this phase of the disease always do well. In the years between 1947 and 1948, surgical intervention was insisted upon only during this stage by our resident staff. As a result of this, there were no deaths during this period of time in which 43 patients were operated upon for perforated peptic ulcer.

The third stage following a perforation is the stage in which peritonitis sets in. These patients are those in whom the diagnosis was not made early or in which neglect occurred. The mortality rate in this group is high.

Although these stages are fairly well defined in any case of peptic ulcer perforation, there are some patients in whom it is extremely difficult to demonstrate them. The high mortality rate associated with the shock state makes it incumbent upon all surgeons to think of these phases when confronted by any patient suffering from a perforated peptic ulcer. The "golden period" for surgical intervention is the reaction stage in which the patient has recovered from the shock of the perforation and yet peritonitis has not set in.

SUMMARY

1. A subnormal temperature in a patient with a perforated peptic ulcer should be considered a manifestation of the shock state.

2. Fifty per cent of all deaths in patients with perforated ulcers were found to be due to shock.

3. The optimum time for surgical intervention is during the stage of reaction. There were no deaths in a series of 43 consecutive patients operated upon between the years of 1947-1948, during this stage.

THE EFFECTS OF VARIABLE INTERVALS OF COOLING UPON THE RESPONSES OF THE LAPIN INTESTINE AND UTERUS AND THE FELINE INTESTINE TO HISTAMINE, ACETYLCHOLINE, PITUITRIN AND BARIUM CHLORIDE

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THE EXPERIMENTS herein reported represented an attempt to repeat in part results described by Ambache in 1946 (1). He determined the responses of small intestinal strips of the rabbit, mouse and guinea pig to various drugs and cations and then studied the effects upon those responses of various periods of cooling in Tyrode's solution (0-2° C) up to eight days. The longest interval applied only to the more durable rabbit gut. The gut of the mouse yielded no responses after more than a few hours of cooling; the gut of the guinea pig was intermediate in its viability. From these results he concluded that the neurogenic components of the gut degenerated more rapidly than the myogenic and that on that basis the actions of drugs might be distinguished that acted directly on the muscle, such as acetylcholine in higher doses, from those acting through a release of endogenous acetylcholine, such as barium ions and histamine. He noted that the responses to the last two stimulants disappeared first, as the period of cooling lengthened, since they depended for their effects upon the integrity of Auerbach's plexus in the gut. Higher doses of acetylcholine, on the other hand, acted directly upon the musculature and so continued to cause responses until the muscular elements themselves had degenerated.

METHODS:

The arrangements in our laboratory for studying the action of isolated tissues have already been described (2). The tissues employed in this study included the small intestine and uterus of the rabbit and the small intestine of the cat.

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The gut of the guinea pig was not studied, since that from our strain of animals has proven almost entirely unresponsive to all stimulants after 12 hours of cooling. In the work with the intestines, but not the uterus, parallel experiments were performed as follows:

1. One of each of the two species was kept in a minimal amount of Tyrode's solution with air overlying the solution;

2. A second pair was kept in Tyrode's solution which had been well gassed with a 95 per cent oxygen — 5 per cent carbon dioxide mixture. In this second case the overlying air was replaced by the same gaseous mixture after which the bottle was tightly stoppered. The pH's of the solutions were taken at the end of the experiment and compared with that of freshly made Tyrode's solution.

For each day's work successive 2 cm. segments of each gut were removed, beginning with the ileal end. That was designed, insofar as possible, to eliminate as a variable in the study the gradient of diminishing intestinal activity from duodenum to ileum (3). The drugs studied included acetylcholine hydrobromide, histamine diphosphate, surgical Pituitrin and barium chloride.

RESULTS:

The results have been summarized in Tables 1-3; at the end of the experiment the pH of the Tyrode's solution with the feline gut exposed to air was 7.63, that exposed to oxygen with CO_2, 6.78, and that of Tyrode's without tissue, 8.28. The corresponding figures for the lapin gut were 8.01, 6.87 and 8.28. The pH of fresh Tyrode's solution is 8.0. It would appear the tissue was per se a better buffer than the Tyrode's solution, a not unexpected result in view of the very weak buffering capacity of that solution. The solution exposed to oxygen and carbon dioxide maintained a lower pH as expected. The pH changes themselves can probably be viewed as inconsequential for isolated tissues, a conclusion confirmed by the remarkable parallelism in the rates at which the re-

TABLE I

CHANGES IN THE RESPONSES OF ISOLATED TISSUES TO DRUGS AFTER VARIABLE INTERVALS OF COOLING

LAPIN GUT

Gaseous Phase	*Hours 0-2° C*	*Histamine*		*Acetylcholine*		*Pituitrin*		*Barium Chloride*		*Remarks*
		Dose	*Response*	*Dose*	*Response*	*Dose*	*Response*	*Dose*	*Response*	
AIR	0	40	***	0.2	***	0.4	– – –	100	**	
O_2-CO_2	0	40	***	0.2	***	0.4	– – –	100	**	
AIR	24	40	***	0.2	***	0.4	– – –	100	**	
O_2-CO_2	24	40	***	0.2	***	0.4	– – –	100	**	
AIR	50	40	*	0.2	*	0.4	–	100	*	Secondary relaxation after Ach.
O_2-CO_2	50	40	**	0.2	**	0.4	– –	100	*	Segmental movements almost gone — both strips
AIR	74	40	*	0.2	*	0.4	–	100	–	Secondary relaxation after Histamine and Ach.
O_2-CO_2	74	40	*	0.2	*	0.4	–	100	*	Secondary relaxation after Histamine and Ach.
AIR	98	1000	0	0.2	*	0.4	0	1000	*	
O_2-CO_2	98	1000	0	4	*	Not Tested		1000	*	
AIR	120									No Responses
O_2-CO_2	120									

All doses are in microgm./ml. except for Surgical Pituitrin, which is in Units/ml.
* = contraction.
– = relaxation.

TABLE II

CHANGES IN THE RESPONSES OF ISOLATED TISSUES TO DRUGS AFTER VARIABLE INTERVALS OF COOLING

LAPIN UTERUS (NON-VIRGIN)

Hours 0.2° C	Histamine Dose	Histamine Response	Acetylcholine Dose	Acetylcholine Response	Pituitrin Dose	Pituitrin Response	Barium Chloride Dose	Barium Chloride Response	Remarks
1	50	***	0.2	***	0.005	***	100	***	Pituitrin & Barium Chloride elicited chain of responses
22	50	***	5	***	Delayed 0.005	***	Delayed 100	***	See Above
46	50	***	0.2	***	Delayed 0.005	***	Delayed 100	***	See Above
70	50	***	0.2	***	Delayed 0.005	**	Delayed 100	**	Chain of less marked, more widely spaced reactions after Pituitrin & Barium Chloride
99	50	**	2	(*)	Delayed 0.005	*	Delayed 200	*	Same as Above.
143	50	*	2	*	0.005	*	200	**	Same as Above.
166	50	*	500	0	0.01	*	200	*	Same as Above.

All doses are in micrograms/ml. except for Surgical Pituitrin, which is in Units/ml.
* = contraction.
– = relaxation.

TABLE III

CHANGES IN THE RESPONSES OF ISOLATED TISSUES TO DRUGS AFTER VARIABLE INTERVALS OF COOLING

FELINE GUT

Gaseous Phase	Hours 0.2° C	Histamine Dose	Histamine Response	Acetylcholine Dose	Acetylcholine Response	Pituitrin Dose	Pituitrin Response	Barium Chloride Dose	Barium Chloride Response	Remarks
AIR	22	1	***	0.04	***	0.2	———	60	***	Secondary Stimulation after washing out Pituitrin
O_2CO_2	22	1	***	0.04	***	0.2	———	60	***	
AIR	50	1	***	0.04	***	0.2	———	60	**	See above.
O_2CO_2	50	1	***	0.04	***	0.2	———	60	**	
AIR	73	1	***	0.04	***	0.2	———	1000	*	See above.
O_2CO_2	73	1	***	0.04	***	0.2	———	1000	*	
AIR	92	1	*	0.04	*	0.2	–	1000	*	See above.
O_2CO_2	92	1	**	0.04	**	0.2	———	1000	*	
AIR	117	1	*	0.04	*	0.2	–	60	*	Secondary Stimulation after Pituitrin gone
O_2CO_2	117	1	*	0.04	*	0.2	–	60	*	
AIR	141	200	0	0.4	**	0.2	–	60	(*)	
				0.2	0					
O_2CO_2	141	10	***	0.04	**	0.2	–	60	(*)	
		200	***	0.4	**					
AIR	163	200	0	0.4	**	0.2	–	60	(*)	
				0.2	0					
O_2CO_2	163	10	***	0.04	**					
		200	***	0.4	**	0.2	–	60	(*)	
AIR	197	200	0	0.4	*	0.2	–	60	*–0	
O_2CO_2		10	**	0.04	*	0.2	0	60	0	
	197	200	*	0.4	*	0.2	–	60	*–0	
AIR	221	200	0	0.4	(*)	0.2	0	60	0	
O_2CO_2	221	200	(*)	0.4	(*)	0.2	0	60	(*)	
AIR	245									No responses.
O_2CO_2	245	200	(*)	0.4	(*)	0.2	0	80	(*)	
AIR	270									No responses.
O_2CO_2	270									No responses.

All doses are in micrograms/ml. except for Surgical Pituitrin, which is in Units/ml.
* = contraction.
– = relaxation.

sponses of the two differently treated intestines declined.

DISCUSSION:

The decline in the responsiveness of all three tissues to histamine and acetylcholine as the interval of storage at 0-2°C lengthened cannot be viewed as significantly different. Two of the tissues (feline gut and lapin uterus), and to a less extent, the lapin gut, appeared to have lost their sensitivity to barium chloride at a significantly faster rate than they did to the other two stimulants. This would appear to confirm, as Ambache contended, that barium chloride does not act directly upon the muscular contractile mechanism. Our results yield no evidence concerning the mechanism of barium chloride's action. Feldberg and Emmelin (4) in experiments designed to elucidate this mechanism, could find no support for Ambache's hypothesis. In an extensive study of the toxicity of various metallic ions upon fungi, Seifriz (5) concluded their toxicity was best correlated with the physical properties of the respective ions: valence, hydration, solubility, dimensions, etc. Such physical properties probably account for the non-specific effect of the barium ion, since no physiological role for this ion has ever been demonstrated. By altering the potential of the cell's membrane, it could temporarily distort the cell's equilibrium. Some indirect evidence suggests that a disturbance in the local concentration of the potassium ion may be the focus of its action. Capraro and Barilli (6) found the response of the guinea pig's intestine to potassium in the presence of a fixed concentration of barium ion increased within a limited range as the concentration of the potassium ion was augmented. Local shifts in the concentrations of potassium ions have been considered at least partly responsible for the reaction to other drugs. D'Silva (7) and Schwartz (8) first demonstrated on animals that epinephrine causes an increase in the serum's concentration of potassium ion. This was confirmed by Marenzi and Gerschman (9) for animals. Later it was independently shown for man also by D'Silva (10) and by Brewer, Larson and Schroeder (11). The earlier failure to detect an increase in the serum's concentration of the potassium ion in humans (12, 13, 14) had been due to the use of venous blood for analysis. The elevation in the concentration of the potassium ion was so fleeting it could be detected only by an analysis of the arterial blood. It had subsided by the time the blood had arrived at the venous end of the circulation. These facts, with others, have led Brown, Bülbring and Burns (15) to suggest epinephrine may act by altering the distribution of the potassium ion in muscle. It is thus possible that the barium ion may act by causing a shift in the concentration of some other cation. It does seem most unlikely that it acts directly on the cell's contractile mechanism, since the responses to histamine and acetylcholine persisted somewhat longer than did those to the barium ion. That a many fold increase in the dose failed to augment the response of still active tissue indicates that it acts on a labile component or element of the structure, which, once exhausted or destroyed, leaves the barium ion in reasonable doses without a focus of attack. This suggests the focus of the barium ion's action is considerably removed from the final link in the enzymatic chain of reactions terminating in the contractile response.

SUMMARY:

A study was made of the effects of cooling upon the responses of the isolated intestines of cats and rabbits and the isolated uterus of the rabbit to acetylcholine, histamine, Pituitrin, and barium chloride. Since the responses of the tissues to the last spasmogenic agent were characterized by marked tachyphylaxis and an earlier loss than were the responses to the first two, it has been suggested that the focus of the barium ion's action is relatively far removed from the final contractile response. It may lead to an alteration in the local concentration of some other cation such as potassium.

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ACTIVITY OF CASHEW (ANACARDIUM OCCIDENTALE) NUTSHELL OIL IN HUMAN ANCYLOSTOMIASIS

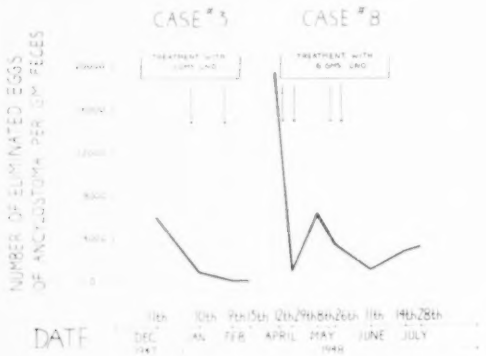
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In a previous communication (1) we reported on the vermicidal activity of cashew (Anacardium occidentale) nutshell oil (CNO) in canine ancylostomiasis. This drug, when given in a single dose of 0.5 to 1.0 Gm. per Kg. body weight, removed 90 to 100 per cent of living Ancylostoma and Toxocara. The vermicidal effect was somewhat lower in other canine helminthiases (Dipylidium, Trichuris). There was no local or systemic toxic reaction even with doses as high as 20 Gm.

These encouraging results prompted us to try CNO also in human ancylostomiasis, especially because the commonly used vermicides are either toxic, as oil of chenopodium, carbon tetrachloride, thymol, or of limited efficacy, as hexylresorcinol and tetrachlorethylene, which are said to remove only 50 to 60 and 60 to 80 per cent, respectively, of the hookworms (2).

METHODS

The clinical experiments were performed on patients of the Medical Department of the "Hospital das Clinicas" of the Faculty of Medicine of the University of Sao Paulo, Brazil. Only such patients who constantly eliminated a high number of eggs were treated. The feces were examined at least three times before treatment in order to establish the constancy of the egg elimination. A saline purgative was administered before stool collection. The results of the treatment were checked by stool examinations seven and 14 days and, if possible, one to two months after the administration of the drug in gelatine capsules (1 Gm. of CNO per capsule). The dose for adults varied between four and six Gm., for children between three and four Gm. The drug was given in the morning on an empty stomach and no food was allowed until noon. If necessary, the treatment was repeated as often as four times in two weeks' intervals.



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In many instances CNO produced a short period of diarrhea, two to four hours after the drug was given. The patients did not have subjective symptoms, except for some heart-burn which passed rapidly.

In one group of patients the stool examinations were performed by counting the eliminated eggs according to the method of Stoll (3). In another group only semi-quantitative examinations were done, classifying the amount of eggs from 1 to 3+.

TABLE I

Case No.	Average number of eliminated worm eggs before treatment	CNO — Total dose — Gm.	Number of administrations	Number of eliminated eggs after treatment	Reduction of worm eggs — %
1	6,300	19	4	0	100
2	700	14	3	0	100
3	6,000	10	2	0	100
4	1,800	16	3	0	100
5	5,200	10	2	0	100
6	3,600	15	3	300	92
7	45,000	18	4	6,800	85
8	19,000	24	4	3,300	83
9	37,500	18	4	300	99
10	13,600	24	4	3,000	78
11	5,600	24	4	0	100

TABLE II

Case No.	Elimination of eggs before treatment	CNO — Total dose — Gm.	Number of administrations	Elimination of eggs after treatment	Result
12	+++	9	3	0	+
13	+	12	4	0	+
14	+	12	4	0	+
15	+++	14	3	+	+
16	+++	5	1	0	+
17	++	5	1	0	+
18	++	5	1	0	+
19	++	5	1	0	+
20	+++	15	3	+++	−
21	+++	13	3	++	−
22	+	5	1	0	+

Results

The results obtained in both groups are shown in Table I and II, respectively. The gradual decrease of worm eggs in one cured and one resistant case is illustrated in Graph I.

It may be mentioned, that in three cases of Ascaris-infestation* we obtained 100 per cent reduction of the egg count in one, 90 and 86 per cent reduction of worm eggs in the other two cases. In three cases of Trichuris-infestation CNO led to the complete disappearance of the eggs.

DISCUSSION

Human ancylostomiasis was cured in 14 out of 22 cases by repeated oral applications of Cashew Nutshell Oil. It seems worth mentioning that all the five refractory cases belonged to the same family, in which some other individuals refused treatment. The high resistance of these patients to the treatment may be explained not only by the extremely high number of parasites (up to 45,000 eggs per Gm. of feces) but also by the possibility of domestic reinfection. This view is also supported by the fact that ascaris eggs, absent at the initial examinations, appeared two weeks after treatment in two of these cases.

Since toxicological studies in dogs revealed that more than 1.0 Gm. CNO per Kg. body weight are well tolerated (1), it seems possible that the optimal clinical doses are above those used in our experiments. Furthermore it is possible that better results could be obtained by shortening the interval between the administrations or by a combination of CNO with hexylresorcinol, in view of the fact that the ascaricidal activity of hexylresorcinol is increased by its combination with cashew nutshell oil (4).

*The number of eliminated worm eggs per Gm. feces before treatment was 10,500; 14,500 and 68,200, respectively.

SUMMARY

1. Cashew nutshell oil (CNO) has a vermicidal effect in human ancylostomiasis.

2. With an average total dose of 13 Gm. divided in three single doses given at intervals of two weeks, a complete cure was achieved in 64 per cent of the cases. In the remaining 36 per cent the number of eliminated eggs was reduced by 78 to 99 per cent of the initial count.

3. In three cases of Ascaris and three cases of Trichuris infestation very marked vermicidal effect was observed.

4. Cashew nutshell oil has a mild purgative effect. No toxic symptoms were observed.

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DIFFERENTIAL DIAGNOSIS OF OBSTRUCTIVE JAUNDICE

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DURING RECENT YEARS the literature concerning jaundice has become almost voluminous and yet obstructive jaundice still remains a problem which at times taxes the ingenuity and diagnostic acumen of even the most astute clinician. Jaundice exists when there is a staining of the body tissues and fluids with bile pigments (1). The terms obstructive jaundice and surgical jaundice have been said to be synonymous. However, experience has taught that obstructive jaundice may be either intra- or extra- hepatic. It is therefore obvious that any consideration of obstructive jaundice must include the medical as well as the surgical type, since at times varying degrees of both conditions may co-exist.

Lichtman states that, regardless of the mechanism by which jaundice is produced, its effects are due to three factors always present in the jaundiced organism (2).

1. Retention of the constituents of bile in the blood and tissue fluids.

2. Complete absence of, or decrease and alteration of bile entering the intestinal tract, and

3. Liver injury.

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Medical or intrahepatic jaundice is associated with degeneration of liver parenchyma and hepatitis. This may be caused by infection or hepatoxic agents such as the arsenicals, cinchophen, liver extract, hypertonic saline intravenously and alcohol. It is well to note the number of cases of serum hepatitis which manifested jaundice during the late war. Possibly the obstruction here is a mild cholangiolitis rather than liver cell degeneration. One must also consider hemolytic jaundice in any attempt at differentiation. In simple hemolytic jaundice, pruritus of the skin and bradycardia are absent, anemia is present. In the progressive stages the jaundice deepens, splenomegaly develops and the patient becomes restless and complains of headache, malaise and epigastric pain. This condition is found in congenital or acquired hemolytic jaundice, occasionally in pernicious anemia and paroxysmal hemoglobinuria.

Infectious or catarrhal jaundice which follows typhoid, scarlet fever or pneumonia must also be considered. Here we may have a complete regeneration of liver cells and a return to normal liver function. The usual findings are slight and may consist of epigastric tenderness, pain, malaise, jaundice, bradycardia and nausea. The associated findings are clay colored stools, urinary bilirubin, leucine, tyrosine and the usual findings of nephritis. There is also an increase of urobilinogen in the urine.

Obstructive jaundice does not manifest the early anorexia and malaise so often associated with diffuse disease of the liver parenchyma. The most common causes of obstructive jaundice are stone in the common duct or in the biliary tract, carcinoma of the liver, and carcinoma of the head of the pancreas. The obstruction may be anywhere along the biliary tract from the cholangeols to the ampulla of Vater. In order to arrive at a diagnosis of any condition one must always have a history. A very precise and full history is perhaps more important than anything else.

The physical examination contributes relatively little to the diagnosis. The most important physical finding when it occurs, is the Courvoisier gallbladder. Palpation of the liver, whether large or small, firm or soft, smooth or irregular, is usually of little help. Distinct, palpable nodules, however, often indicate metastatic carcinoma which by involving the bile ducts may be the cause of obstructive jaundice. A palpable mass in either the abdomen or the pelvis must be sought in order to rule out primary neoplasm of the gastro-intestinal tract. A palpable spleen is very suggestive of liver degeneration.

Other features such as the color and intensity of the jaundice and the development of itching do not help to differentiate extra- from intra-hepatic jaundice.

While in recent years there have been developed numerous valuable laboratory tests which are of great help in making a diagnosis, their very multiplicity indicates that none are uniformly satisfactory and every test so far introduced occasionally fails. As in many other conditions, laboratory tests may be of use in forming a clinical impression, but not to make diagnosis. The oldest and one of the most important tests is that of the stool to determine whether or not any bile is entering the intestinal tract. Here the test is for urobilin and a gray or white stool is nearly always negative. The stool should be examined frequently.

A more direct way of determining whether bile is entering the intestinal tract is by means of the duodenal tube. This test is more direct than the examination of the stool. However, the fluoroscope should always be used here to determine the position of the tube. The most constant single sign of neoplastic obstruction to the bile passage is complete absence of bile from the duodenum (3). The advantage of the stool examination over the duodenal tube is that it can easily be repeated daily.

The urine should always be examined for urobilin and urobilinogen. Complete absence of these substances indicates total acholia of the stools.

The persistent and total absence of bile for six or seven days is usually the rule in malignant obstruction of the bile duct. An occasional exception is due to secondary ulceration. Transient absence of bile occurs in obstruction by stone and in suppression due to hepatic degeneration. Total absence of bile is common enough in hepatic degeneration, however, it is nearly always transient. The determination of the serum or plasma bilirubin should be repeated frequently. Whether the Van den Bergh reaction is direct or indirect is of little value in differentiation. Both obstructive and hepatic jaundice produce the direct Van den Bergh.

In Rich's classification (3) he divides jaundice into the retention and regurgitation groups and there is little difficulty in differentiating one group from another. However, the forms which are hard to differentiate are the regurgitation group. Since these all give the direct Van den Bergh reaction in serum as well as bilirubin and bile salts in the urine, these tests are of little value in differential diagnosis.

The quantitative Van den Bergh is almost specific for bilirubin. The disadvantage is, that it is a precipitation method and that an unknown and highly variable amount of bilirubin is always lost in the precipitation.

The icterus index is more important than the Van den Bergh test for the determination of the blood bilirubin and even more important are the variations of this level from day to day. Because of this and its simplicity, it is to be preferred. The important practical point is that the blood serum must be collected without hemolysis.

Experience has shown that in following the course of a mild or slight jaundice and especially in detecting the so-called latent jaundice, the qualitative Van den Bergh is misleading as compared to the icterus index. A constantly high icterus index indicates a complete obstruction due to neoplasm, while a stone in the common duct usually causes a fluctuating index.

The flocculation tests may be done, but they are not specific and only measure certain phenomena associated with changes in the plasma proteins (4). A weakly positive test is of little significance; a strongly positive test indicates damage to the liver parenchyma. A negative test favors diagnosis of obstruction to the common duct.

The determination of the cholesterol of the blood plasma is of great differential value. The normal blood cholesterol is about 200 mgm. per 100 cc. of blood. The level increases greatly with obstruction, up to 300 mgm. to 400 mgm. or more and remains so until late in the disease. In severe liver degeneration there is a marked drop and this is of considerable prognostic importance. Other causes of increased blood cholesterol are few. The important ones are nephrosis and uncontrolled diabetes. The determination of the cholesterol esters in the blood plasma is of considerable value as a diagnostic criterion. Normally two-thirds to three-fourths of the blood cholesterol is in the form of cholesterol esters.

In obstruction of the bile ducts the increase of cholesterol esters is parallel although not so great as the increase in cholesterols. In hepatic degeneration, the cholesterol esters tend to fall and in severe cases often completely disappear. The persistence of cholesterol esters in the presence of jaundice is of grave prognostic importance, indicating serious damage of liver parenchyma. It is of special value in making the correct diagnosis in those early cases of catarrhal jaundice which ultimately go on into acute yellow atrophy of the liver. Cholesterol esters may also drop in cases of obstructive jaundice when extensive liver damage or degeneration supervenes to close the scene. These tests, although of great value, should never be used as a single and specific mode of differentiation and must always be interpreted in the light of the clinical features of the case.

In spite of its limitations one of the best tests for liver function is the galactose tolerance test. This test

depends on the fact that the liver converts galactose into glycogen and ultimately dextrose and the kidney has no threshold for galactose. So long as there is galactose circulating in the blood, some of it is excreted in the urine. The normal excretion of galactose by an undamaged liver is three grams or less. The galactose tolerance test is positive in most cases of deep jaundice due to disease of the liver parenchyma. There are many exceptions and a negative result is not indicative of obstruction. The test frequently fails in undoubted liver degeneration. However, when diabetes can be ruled out, a positive galactose usually means hepatic degeneration.

The alkaline phosphatase test is elevated in obstructive jaundice and high levels persist until the jaundice subsides. There is a slight or moderate increase in diffuse hepatitis. According to McLagen: "The phosphatase test in connection with the thymol turbidity test will differentiate obstructive from non-obstructive jaundice in 80 per cent of cases" (5).

A prothrombin time is essential in the study of every jaundice patient. If an elevated time is found, one may readily distinguish obstructive from parenchymatous jaundice by giving an intravenous dose of one of the substitutes for Vitamin K. If the test is then repeated in two to four hours, biliary obstruction is evidenced by a marked reduction in prothrombin time.

The x-ray has little to offer in obstructive jaundice. A simple flat plate of the abdomen should, of course, always be done and may reveal pancreatic or biliary calculi. However, cholecystographic technique does not permit visualization of the gallbladder in the presence of occluded bile passages or hepatic damage. Cases in which it is difficult to make a diagnosis are those of metastatic new growths causing either complete or partial obstruction by involvement of the bile ducts in the liver itself or in the hilus. The diagnosis is made only if the primary growth is found after a careful G.I. series, sigmoidoscopy and barium colon enema.

It is assumed that the routine urinalysis, hemoglobin, blood count and tests for syphilis are routinely done.

Conclusion

After attempting to evaluate and interpret a number of tests it must be remembered that there is a small group of jaundiced persons in whom diagnosis resists the usual investigative methods. Here the practitioner must often rely on the history, physical examination and bedside observations. A neoplastic obstruction may produce a confused picture, yet frequently the course is characteristic. It is in these cases that a diagnosis is often made by clinical experience and keen observation together with laboratory evidence. Since it is known that an obstructive jaundice which persists for six weeks will be complicated by liver cell degeneration, surgery may finally be necessary in order to determine the cause of the jaundice.

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DIVERTICULA OF THE STOMACH

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DIVERTICULA of the gastrointestinal tract are most common in the colon, but they occur also in the oesophagus, the duodenum, the stomach and the ileojejunum. The diverticula of the stomach are comparatively rare. Rivers, Stevens and Kirklin from the Mayo clinic have only reported about ten cases, which had been removed at 11,234 exploratory operations of the stomach. Resnick has found three cases of true diverticulum in 1,000 consecutive examinations of the gastrointestinal tract with barium contrast. Martin collected four cases in the literature, in which two or more stomach diverticula had been present simultaneously with one patient. Concomitant diverticula in other parts of the intestinal tract of the same patient have been detected in 12 per cent of the cases (Reich).

The majority of the gastric diverticula present themselves juxta- or paracardiacally, near the cardiaoesophageal junction and at the posterior aspect of the stomach. Only comparatively few parapyloric and prepyloric diverticula have been reported (Tracey).

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The beginning and development of the gastric diverticulum is in most cases so insidious and inocuous, that the patients frequently are unable to give definitive data. This abnormality is mostly discovered in adult life, in the majority of cases in women of forty or older, but cases with younger individuals and even in babies have been described.

The symptoms, which have been found prevalent in these cases may be listed as 1) dull, dragging pain in the epigastric region and nocturnal distress, 2) discomfort and feeling of pressure in the upper abdomen, four to five hours after meals, 3) periodic burning and gnawing pain, sometimes relieved with the intake of food. The pain radiates often to the lower substernal region. 4) malaise, which is relieved with bicarbonate, to induce vomiting, whereafter the symptoms ease up, 5) vomiting, which may contain food particles, taken up to twelve hours previously, 6) belching, bloating and rumbling in the abdomen, 7) bloating sensation, which wakes the patient up at night, and 8) massive hemorrhages.

The size of the diverticulum and its character are responsible for and may influence the prevalence of the various symptoms, but some of the symptoms, attributed to the diverticulum, may be the result of associated ailments.

In the differential diagnosis, the following conditions must be considered: diaphragmatic hernia, diverticulum of the oesophagus, malignancy, perforating ulcer of the stomach and a Haudek's niche. The diverticulum may become inflamed and then symptoms may occur, which increase the difficulty of the diagnosis.

In a series of 1,000 gastroscopies, Schindler found three cases of diverticulum and could visualize them. Tracey warns of the dangers of a gastroscopy on account of the unknown character and resistance of the wall of a diverticulum, which might be perforated at this examination, f. i. in the case of a myomata in the diverticulum. No report of a perforation at this examination has been found.

The diagnosis can best be established by x-ray examination. A routine gastro-intestinal examination reveals often a diverticulum of the stomach. In case there is suspicion of the abnormality and the routine examination is negative, x-ray of the stomach, taken in different positions of the patient, horizontal, vertical or oblique, might be instrumental in demonstrating the diverticulum. An oblique picture may even produce the pedicle of the cul-de-sac, occasionally a fluid level could also be visualized. Irregularity of the wall may mean malignancy.

The classic differentiation of all diverticula is congenital or true and acquired or false diverticula. The differentiation is rarely substantiated by clinicopathological examination, because the cases either did not come to visualization at an operation or no pathological examination could be performed.

The explanation which is given as to the cause of the development of a diverticulum is more or less hypothetical, but it may be well worthwhile, to give a short resume of the different theories.

A congenital or true diverticulum is a pouch-like formation of a part of the intestinal tract. All layers of the tract, from where the diverticulum originates, are present in the pouch or diverticulum. This true diverticulum, presenting itself as a blind tube, has been observed most commonly in its typical formation in the jejunum, called Meckel's diverticulum. A case of a true diverticulum of the paracardiac region has been described in an embryo.

According to Frank and others the majority of diverticula, which are found in the paracardiac region, are pulsions diverticula and also of congenital origin, caused by a congenital malformation or at least weakness of the musculature in that region. This local weakness is explained by some authors by the special alignment of the muscle fibers. The intragastric pressure is assumed to bulge the mucosa of the stomach through the thinned and therefore weakened lines of muscle fibers in that specific region. This constant intraluminal push and pulsion against insufficient resistance may create a sac-like evagination interrupting the continuity of the gastric wall. It is perhaps just a matter of time then, whether the examining pathologist finds still remainder of muscle fibers from the longitudinal or oblique musculature of the stomach in the wall of the diverticulum. In further advanced cases, even this thin coat of muscle fibers will be atrophied and only the serosa and mucosa as the only remainder of the wall of the diverticulum are present, so that the diverticulum, presumably, is very thin and collapsible.

Some authors consider the development of a gastric diverticulum as a symptom of degeneration, due to the loss of tone and elasticity of the musculature in the degenerative period of life (Boyd).

According to another theory, the mucosa of the stomach is pressing through the normally existing vascular orifices, where the vessels, accompanied by a sheath of fat, pierce the gastric wall and this hiatus creates the path for the development of a diverticulum.

Boyd mentions further the neuromuscular imbalance, which may develop, when during the normal peristalsis in the involved part of the intestinal tract a wave of relaxation precedes the wave of contraction and between two contracted segments a herniation is formed.

The false or acquired diverticula are sac-like evaginations, which supposedly develop when a force, working from the outside, in form of traction, causes the formation of a diverticulum. A perforating ulcer or strong adhesions have been considered to be causative factors for the formation, called also traction diverticulum. Any of the neighboring organs, which might have been the site of an inflammatory process, may be responsible for the development of perigastric adhesions. The contracture of these adhesions, it is assumed, causes the formation of a diverticulum by mere force of the traction. Jordan and Labey f. i. postulate perigastritis for the formation of a gastric diverticulum.

No case of a dissecting (intramural) diverticulum of the stomach has been described.

In the majority of the cases, the diverticulum has been found to be a smooth, rounded protrusion or projection from the lumen of the stomach. The sac-like formation is usually thin walled, pliable and collapsible. It is formed like a bag, more long than oblique. Diverticula of various shape and size have been reported and demonstrated in x-ray pictures. Either a wide opening or a pedicle, narrower than the length and width of the diverticulum, leads to the pouch. In traction diverticula, there might be no real pedicle, but the diverticulum might look like a fold or protrusion of the gastric wall.

At the diverticula of the colon, the communication between the cul-de-sac and the colon often shrinks and closes up. In this manner, the connection between the pedicle and the pouch is severed. The cul-de-sac will thus be transformed in a cyst, filled with mucoid material and pedunculated with the colon. Such a formation has not been found as yet in gastric diverticula.

As in Meckel's diverticulum, formation of a tumor occasionally develops in a diverticulum of the stomach. Martin collected four cases of adenomyoma, three cases of carcinoma and one case of fibrosarcoma from one hundred cases of gastric diverticulum in the literature. Pancreatic tissue was found quite frequently in the pouch. Benign or malign tumors were present in the majority of the cases in diverticula located in the prepyloric, and very rarely in the paracardiac region.

Like the diverticula of the duodenum and the colon, gastric diverticula often do not produce any subjective or objective symptoms. When, however, therapeutic measures were indicated, conservative treatment proved to be satisfactory in many instances. Low residue diet, antispasmodics and antacids, as powdered bismuth, etc., are recommended in this condition. In other cases, postural drainage has enabled the patient to empty the pouch, often after preliminary fluoroscopic control. F. i., drinking of a glass of water when the symptoms appear and then hanging the head over the edge of a couch, first bending over to the right and then to the left and repeating this procedure three to four times, has brought relief in many cases (Hurst and Briggs). Another successful method of treatment, also of palliative nature, has been described by Reinike. In this case, the patient took small amounts of barium sulphate daily on an empty stomach, to keep the diverticulum filled, before eating.

According to most authors, surgery is only indicated when the diagnosis is in doubt and when conservative treatment has proved ineffective. Extraordinary circumstances, such as severe hemorrhage, or symptoms suggesting impending perforation of the diverticulum, make surgical intervention imperative, although no rupture of a simple diverticulum of the stomach has come to our attention. Figara and others consider that surgery in cases of gastric diverticula is always indicated, because of the high incidence of associated lesions. As late as 1926, many authors have denounced the open operation of a gastric diverticulum as "impracticable and usually impossible." Tracey calls attention to the fact that in many instances the diverticulum could not be isolated or found. Martin has collected 28 cases from the literature which had been operated upon and in three of them, the diverticulum had not been found. Tracey has reported several successful operations of his own cases.

At the present time and with the progress of the abdominal surgery ev. with the transthoracic approach, the location of a diverticulum, even paracardiac, should be no reason not to operate, if there is an indication to do so. Comparatively few reports have been published about the operation of a diverticulum. There are two operative procedures, the excision and the inversion of the evagination. Since, in some instances, the frequently very small pouch has been difficult to find, Ferguson advises to give the patient a glass of bismuth the evening previous to the operation or early on the day of the operation, to give the cul-de-sac a white lining for identification. This seems effective only in the case of a thin walled diverticulum, which is more or less translucent. Some authors favor the invagination as the type of operation in those diverticula which are located near the cardia, because it certainly is a relatively simple procedure. We believe that the clinical finding should be considered. In the case of a paper thin, collapsible pouch, which is therefore more or less translucent, the invagination of the cul-de-sac seems to be a very good operation. Ferguson and Cameron and others have reported good results with this procedure. However, in cases where the diverticulum has walls which are not translucent, the excision of the pouch seems advisable in order not to overlook a malignancy, which might exist inside the diverticulum. As has been mentioned already, it is prevalent in the prepyloric region that a malignant growth had developed associated with the diverticulum.

Most cases that have been reported have been symptom free after the operation, but Martin has collected 28 cases from the literature; from these only 64.3 per cent had become completely cured.



Figure 1. — A large diverticulum at the beginning of the lesser curvature of the stomach, just below the cardia.



Figure 2. — After three hours, the stomach retains a trace of the barium, but the diverticulum is completely filled.



Figure 3. — After six hours, the barium is still in the diverticulum.

Case report: Mrs. J. M., a 40 year old woman, weighing 160 pounds, married and the mother of a ten year old daughter, was referred to us on October 7, 1948. Her chief complaints were heavy feeling in the abdomen, dizzy spells and a foul taste in her mouth, especially in the morning. Occasional spells of vomiting in the morning brought up sour and foul tasting material. Additional history revealed complaints of feeling like "blown up" after meals, episodes of dyspepsia and heartburning. She had consulted many doctors and had been given various kinds of treatment and drugs without obtaining relief. During the last ten years severe gastrointestinal examinations with contrast material allegedly had not revealed any abnormalities in the gastro-intestinal tract.

When this patient came to Dr. H. R., he had another series of x-rays taken by Dr. E. G. on June 15, 1948. At that examination, a large diverticulum of the stomach was found at the beginning of the lesser curvature, just below the cardia (Fig. 1). The remainder of the stomach proved to be normal; there was only a suspicious indentation near the cap, suggesting a minute duodenal ulcer. The diverticulum of the stomach was still fully visualized after 24 hours (Fig. 3).

Further medical treatment did not bring sufficient relief. On September 29, 1948, a further radiological examination demonstrated again the large gastric diverticulum, but there was no further evidence of the previously reported niche formation at the duodenum. There was the additional evidence of two small diverticula of the colon (Fig. 4).

In consideration of the long drawn history of unsuccessful medical treatment, the operation of the diverticulum was decided upon. The patient was admitted to a private hospital on October 15, 1948. The laboratory tests showed 80 per cent Hemoglobin, 4,600,000 red blood cells, 7,850 white blood cells, 69 per cent neutrophiles, 28 per cent lymphocytes two per cent eosinophiles. The urine was negative for sugar and albumen.

On October 17, 1948, the right upper abdomen was explored by a transverse incision under spinal anesthesia, which had to be supported by intravenous pentothal. Excessive fat of the omentum was encountered. The stomach and the adjoining duodenum did not reveal any sign of ulcer or other visible pathology. Even after wide freeing of the major and lesser curvature of the stomach, the diverticulum could not be visualized. The anterior aspect of the stomach was



Figure 4. — Two diverticula in the colon.

therefore opened by a small incision. The examining finger could then locate the sharply circumscribed opening of the diverticulum near the cardia. Thereafter, the small, paper thin pouch of the diverticulum could be found high at the lesser curvature; it proved to be a sac, one and one-half to one inch wide, translucent and collapsible. In consideration of the location and the translucency, it was decided to invert the diverticulum. This was accomplished by two rows of black silk. The closure of the stomach and the abdominal wall were uneventful.

Postoperatively, the temperature rose to 102 rectally on the second day. 300,000 units of Penicillin were given for two days. The patient was out of bed on the fourth postoperative day, and was discharged from the hospital on the seventh postoperative day.

According to the latest report, fifteen months after the operation, her symptoms have disappeared and she is cured.

Comment: A case of a paper thin diverticulum of the stomach, located near the cardia, was operated upon by invagination with a very good result. The presence of two small diverticula of the colon was noted. The complaints of the patient had been rather vague and previously taken x-rays of the stomach had not revealed any pathology, which might have justified the subjective and objective symptoms which she presented. No adequate anatomical reason could be found for her complaints. Her ailment was considered to be a nervous stomach and the case more or less judged as belonging to psychosomatic medicine. Only after long drawn unsuccessful treatments and observations was the diverticulum of the stomach discovered. Most probably, the cul-de-sac formation of the diverticulum was not so far advanced that the barium contrast material remained visible at the previous examinations. After the outpouching had been so extensive and sufficiently enlarged that the barium remained in the pouch, the evagination could be detected. The disappearance of her complaints after the operation stresses again the necessity that one can not be too careful in diagnosing a patient as a neurotic when no explanatory data for his complaints can be found.

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A POST-OPERATIVE ANALYSIS OF THE GASTRIC CHEMISTRY IN CASES FOLLOWING GASTROENTEROSTOMY AND PARTIAL GASTRECTOMY FOR DUODENAL ULCER. INFERENCES ON FAULTY SURGERY IN RELATION TO POST-OPERATIVE SYMPTOMATOLOGY

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IT is no easy task to obtain an adequate follow-up of postoperative cases when patients are, at least to their own satisfaction, free from symptoms. This point was well demonstrated in a study from my private files. It became apparent that the patients who volunteered their visits were those who had recurrent clinical manifestations of a digestive aberration, and were cases of gastroenterostomy. Among the partial gastrectomy patients, however, some did respond to a follow-up procedure, while others treated the communication they received with entire indifference. This lack of concern may have been due, in part, to the disagreeable memories of the intubation used to determine their gastric chemistry; in part by their feeling that they were free from symptoms of any disorder. To the writer these patterns of postoperative response from the two types of patients suggest the marked superiority of partial gastrectomy over gastroenterostomy. It is generally agreed that an asymptomatic patient is a noncooperative individual. When there was present the added factor of a personality insensitive to pain, this type of patient, in my observation, resented an inquiry into his postoperative digestive clinical demeanor.

Some writers maintain that gastroenterostomy performed for duodenal ulcer in patients having hypersecretion and hyperchlorhydria produces a true and sustained achlorhydria. This belief was well demonstrated in the cases to be presented briefly in this paper. It is regrettable that in almost all of my cases of the simple anastomotic operation, shortly postoperatively it was not possible to ascertain whether an early achlorhydria had replaced the preoperative high HCL values. Considering the factors conducive to achlorhydria, such as rapid gastric clearance through a large stoma, site of anastomosis in vertical axis of the stomach, and reflux of bile through the ascending limb of the gastroenterostomy, hypochlorhydria or total absence of acid is a possible phenomenon. In contrast it has been shown that there is a higher incidence of postoperative ulcerations after an anterior type of anastomosis because the stoma is not as efficiently bathed in alkaline juices as the stoma of a posterior gastrojejunostomy, and, an anterior anastomosis requires a longer jejunal loop, thereby increasing the influence of the acid-pepsin factor in ulcer genesis. Whether or not the patient had had a postoperative transient achlorhydria which yielded four or five years later to evidence of high HCL values, could not be definitely stated. One might indeed argue that the reason some of the simple gastroanastomotic cases did not present themselves for earlier examination was that they were asymptomatic—a phase of silence or quiescence engendered by an earlier gastric secretory depression. It should be stated that an early postoperative gastric analysis for detection of a transient achlorhydria is obviously a desirable procedure. Whether or not this achlorhydria did exist, the important fact is that it was, in any event, transient.

The following cases have been selected to exemplify the types of symptomatology and gastric chemistry in postoperative simple gastroenterostomy and partial gastrectomy.

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CASE REPORTS

Case I. Male, age 43 at time of operation, January, 1944. Clinical picture classically descriptive of a post-pyloric lesion. Repeated gastric analyses yielded HCL values, highest 72 units, lowest 46 units; total acidity values, highest 92 units, lowest 76 units. Roentgen evidence of duodenal deformity but no six hour gastric residue. Marked intractability conditioned this patient who submitted to operation. "Pre-operative diagnosis: Pyloric stenosis. Post-operative diagnosis: Benign pyloric stenosis. Name of operation: Posterior retrocolic Gastroenterostomy."

10/15/49. Patient complained of attacks of pain in left abdomen for several weeks, which mostly occurred during sleep. Diurnally he noted pre-meal distress and food ease. Gastric analysis yielded free HCL 69 units, total acidity 89 units.

X-ray of operative field showed the following points of interest: 1) the opaque medium passed unhesitatingly through the stoma, 2) pylorus was not obstructed by the original lesion, 3) efferent jejunum was much dilated but narrowed at its midportion, constant on all films.

Comment: Interpretation of the roentgen findings and a consideration of all the circumstances in the case, indicated that a diagnosis of an anastomotic ulcer caused by acid regurgitation was tenable, and cast doubt on the validity of simple gastroenterostomy.

Case II. Female, age 56 at time of first examination in 1936. Her history revealed that she had long had a rumbling abdomen which was neither toned down by previous appendectomy, nor silenced by gastric surgery for a post-pyloric lesion in 1935. Report reads: "Stomach, duodenum, gall bladder and colon all adherent to abdominal wall. First inch of duodenum had an old callous ulcer. After letting down all adhesions, did a very satisfactory posterior gastrojejunostomy, also let down ligament of Treitz for several inches." Against this surgical background might be pitted the pre-operative clinical picture which on careful scrutiny, was devoid of clinical criteria in favor of a duodenal ulcer. Had the supremacy of the history been reckoned with, surgery would never have been performed. The surgeon "preferred a gastroenterostomy because of technical difficulties."

Gastric analysis — one year post-operatively — showed free HCL 47 units, total acidity 67 units. Roentgen survey of the gastrointestinal tract showed the barium passed rapidly through the gastroenterostomy stoma, and the duodenal cap filled and was smoothly outlined. Thus two avenues of exit operated in this case, rendering her gastric drainage too rapid and accounting for the sameness of pattern in all those post-operative years, taking on criteria of a dumping syndrome.

Comment: This case demonstrates a clinical failure in response to a simple gastroenterostomy. The operation brought her rattling non-complacent abdominal viscera into greater prominence and her pre-operative dyspepsia was enhanced by a surgical procedure which proved to be a disease rather than a cure. It is hard to argue that had a subtotal gastrectomy been done with a normal anastomotic stoma, this patient would have become eupeptic. This is speculative indeed. It is to be noted that her gastric chemistry was within normal range one year post-operatively, and two years later on repeated tests and following an alcohol test meal, a sustained achlorhydria was evident achlorhydria of advanced age. HCL therapy had but relatively silenced her symptoms of dyspepsia.

Case III. Male, age 41. Ten years previously he had had an appendectomy and six months after had passed "jet black stool." A roentgenologic study showed a duodenal deformity. A gastroenterostomy was performed. When the patient was examined by the writer he described a classic rhythm of a post-pyloric lesion for a period of 18 months, topped with nocturnal episodes of pain, periodicity and intervals of freedom from symptoms. He also complained of intestinal uneasiness, nausea, epigastric distress and a sinking feeling. Gastric analysis showed acid values within normal range, but contents were mixed with frank bile. It was suggested by an appraisal of the clinical picture that he probably had a high gastric acidity, which after was lowered by the reflex buffer bile. Roentgenoscopy showed a large anastomotic stoma placed at the most dependent part of the lower pole of the stomach. Evacuation was not intermittent. The distal jejunal limb proximal to the stoma was considerably dilated. The barium was also seen passing through the duodenum. Cap was not filled in its entirety.

Comment: It is apparent that in this case the gastroenterostomy caused a train of disturbances. The food poured straight through the high mal-placed stoma into the jejunum and overloaded it. After 14 post-operative years it is reasonable to conclude that the stoma had not sphincteric attributes, thus another anatomical cause for dumping was added. The operation in this case was rewarded by recurrence of symptoms, a functioning stoma but too rapidly emptying of gastric contents. Psychologically a disappointed patient.

Case IV. Male, age 45, presented a history of long chronicity descriptive of a duodenal ulcer. Gastric analysis yielded high acid values — HCL 66 units, total acid 110 units. Roentgenologic examination yielded evidence of bulbar deformity with a large six hour gastric residue. Operative findings (June, 1936): "Callous ulcer on posterior wall of the duodenum. Technique: Posterior short loop gastroenterostomy." Six months post-operatively gastric analysis yielded values of benign achylia. The patient complained of hunger episodes with symptoms of syncope. He related the following: "All of a sudden I get a sense as though I lost my balance under my feet, I feel loss of strength and immediately feel relieved by eating." On inquiry these spells had a definite relationship to food ingestion — from one-half to three-quarters hours p. c. Patient learned — own advisement — to equip himself with chocolate when away from his home and he would resort to it at the slightest sense of an oncoming "sinking." On one occasion when he failed to have the chocolate on his person, he felt a sense of nausea and lightheadedness, but was able to reach a store and request immediate attention. He was promptly relieved by a glass of chocolate.

Roentgenologic examination of the anastomotic stomach showed a rapid outpouring of food through the duodenum. Fasting blood sugar showed 55 mgs. per 100 cc. A blood sugar tolerance plotted a hypoglycemic curve: Fasting — 79 mgs. per cent, 30 minutes after glucose intake — 166.7 mgs. per cent one hour after — 131.6 mgs. per cent two hours after — 78.6 mgs. per cent, three hours after — 66.0 mgs. per cent.

Test repeated: Fasting stomach blood sugar 81.3 mgs. per cent. After ingestion of 100 grams dextrose: After 30 minutes — 146 mgs. per cent, after one hour — 117.6 mgs. per cent, after two hours — 82.4 mgs. per cent, after three hours — 55.2 mgs. per cent.

Comment: The dumping syndrome in this case expressed itself in a clinical picture of hypoglycemia. The patient responded to a dietary regimen of high protein, high fat and low carbohydrate. The large size of the anastomotic stoma was held accountable for his dumping syndrome manifested in the pattern of hyperinsulinism engendered by too rapid absorption of carbohydrates. The size of the meal and intensity of symptoms became apparent, and frequent small meals added much to alleviation by diminishing mechanical distention of the jejunum — an environment anatomically and physiologically unsuited to sudden distention by unchymified food. It was of interest to note that on resuming activity — an occupation that required walking — immediately after meals he experienced bizarre symptoms of abdominal distention, and that rest after meals added much to his comfort. Culver (1) writes: "It has been suggested that physical exercise increases the consumption of glucose and there is a more profound hypoglycemia as a result of insulin stimulation by food." This phenomenon is well demonstrated in this case. The component pain in the pre-operative ulcer rhythm was replaced by lightheadedness to mean sense of fainting. In contrast Alvarez (2) asserts it difficult "... to believe that a lowered blood sugar content could have anything to do with the dumping syndrome." The behavior of ready response to ingestion of candy or fruit juices, in this case, takes the guessing out of empiricism.

Case V. Male, age 28 when first examined in 1924. He then presented a clinical picture of a tense individual strongly possessed of economic "drive." He related symptoms of dyspepsia but lacking the orthodox pattern of a post-pyloric lesion. Ewald test breakfast showed free HCL 59 units, total acidity 97 units. A report from the Boston City Hospital read: "6/1/25. Report on X-ray Examination. Shows stomach atonic with sluggish peristalsis; its outline is regular. Duodenum is irregular, but does not show the typical

deformity of ulcer and is probably due to adhesions. At five hours stomach is practically empty. At 24 hours head of meal is at rectum. Appendix is freely movable and not tender. Cecum is regular in outline. Colon not remarkable." Repeated x-ray survey at Fordham Hospital 1933 and at writer's office 1941 showed duodenal deformity. In correlation: gastric analysis yielded HCL values: lowest 50 units, highest 69 units, total acidity lowest 85 units, highest 97 units. Nocturnal episodes of pain, periodicity and intractable chronicity punctuated the clinical picture and, resident in a host who had cooperated remarkably in a medical regimen, warranted surgery. Since this case was rightly labeled as hypersecretory duodenal ulcer, it was suggested that partial gastrectomy be combined with subphrenic vagotomy to obtain the looked for achlorhydria. Surgical report, Mount Sinai Hospital, New York City, 7/3/47: "A small healed scar in the superior wall of the duodenum, about 2 cm. distal to the pylorus with about four string adhesions around the duodenum, was found. About two-thirds of stomach was cut away. The duodenum was shaved down as far as possible and cut across. A Hofmeister antecolic gastrojejunostomy was done." No vagotomy was done, despite sustained hyperchlorhydria. Six months post-operatively, gastric analysis showed achlorhydria. Contents were strongly bile tinged. Clinically this patient held on — although mildly — to some of his pre-operative symptoms, but it was too evident that he had a very susceptible threshold for pain and that he would not readily divorce himself from such symptoms as intestinal uneasiness and bloating after meals. Three gastric aspirations following test meals, two years post-operatively, showed a well defined achlorhydria.

Comment: This case demonstrates that a continued hypersecretory stomach was reversed by partial gastrectomy to a long sustained achlorhydria. The type of operation per se merits the credit for the anacidity, since a supplementary vagotomy was not done as had been first suggested by the surgeon. I may add that his post prandial distress is adequately alleviated by HCL therapy.

Case VI. Male, age 24 at time of first examination in 1935. He related a clinical history of a post-pyloric lesion dating from 1928. Tube tests and x-ray survey of the gastro-intestinal tract confirmed the diagnosis of a duodenal ulcer. The clinical pattern of a post-pyloric lesion continued. In 1942 the patient again related periods of activity alternating with periods of remission. X ray check-up showed persistent bulbar deformity, but no five hour gastric residue. Repeated gastric analyses: Fasting, lowest free HCL 65 units, total acidity 90 units, highest 98 free and 117 total. Following test breakfast: lowest free HCL 68 units, total 81 units, highest free HCL 84, total 122 units. Intractability called for elective surgery. Report: "Partial gastrectomy, end of stomach to side of jejunum, Polya." Pathological report: ". . . ulceration shows sharp demarcation from the tissue but it is fibrous and is infiltrated by lymphocytes and eosinophiles. Pathologic diagnosis: Benign peptic ulcer of the duodenum."

Seven months post-operatively: Gastric analysis, free HCL 8 units, total acidity 22 units. One year later, free HCL 10 units, total acid 22 units. Clinical picture "not complaining."

Comment: Two gastric analyses post-operatively showed a marked hypochlorhydria. Regrettably this patient was not followed up from then on. It is of interest to note that two brothers were diagnosed as having duodenal ulcer, a point in support of the view that familial diathesis plays a large part in ulcer genesis.

Case VII. Male, 53, first examined in 1947. This patient came for a "general check-up." History revealed that in 1936 he had a copious hematemesis. Duodenal ulcer was diagnosed. A partial gastrectomy was then performed by Dr. Umberto Benedetto, Catania, Italy. The patient had no definite complaints to make. In 1947 Ewald test breakfast yielded low acid values — free HCL 17 units, total acid 28 units, strongly bile colored. Combined roentgenoscopy and roentgenography of the operative field revealed a partial gastrectomy with all roentgen criteria of a normally functioning anastomotic stoma, nondumping. Gastric analysis (1950) showed a total anacidity. A relatively symptom-free patient.

Comment: It was evident in this case that the humoral phase of gastric secretion was eliminated, and that free flow of bile furnished an alkaline bath to the stoma that is necessary for effective neutralization. Blood showed a normal glycemia — added attestation to a normal gastric emptying and therefore no rapid absorption of carbohydrates to provoke insulinogenic reaction. It is apparent in this case that partial gastric resection secured one of its important functions: precluding acid aggression and thus preventing marginal or jejunal ulcer. Three years later gastric analysis showed a total anacidity. It is regrettable that the pre-operative gastric acidity values could not be obtained. Bockus (4) avers, ". . . the presence of true achlorhydria practically excludes the diagnosis of gastro-jejunal ulcer." His warning that "The diagnosis of an achlorhydria after subtotal gastrectomy is not valid unless the tip of the tube is placed within the body of the stomach" was very carefully observed, not, however, under fluoroscopic guide as he suggested.

DISCUSSION

The following points are culled for discussion: 1) Chronicity despite presumably adequate treatment may be accepted as a failure of therapy and an indication for operation. 2) Conservative gastroenterostomy versus partial gastrectomy clinically considered. The objective sought in peptic ulcer surgery is the removal of acid aggression that figures so much in ulcer genesis. A simple gastroenterostomy does not accomplish the objective as is shown by the cases here reported. Partial gastrectomy in this respect proved superior. As regards faulty factors in operative technique — admittedly not a subject for clinical assessment — they are common to both types of operation, as for example, rapid gastric clearance through large anastomotic stoma. Culver (1) states that "The incidence of the 'dumping' syndrome varies from five to 25 per cent of all subtotal gastrectomies for peptic ulcer." In contrast with simple gastroenterostomy he refers to Scandinavian reports suggesting "that the incidence of 'dumping' syndromes may be greater after a simple gastroenterostomy than subsequent to subtotal gastrectomy." As a matter of fact the symptoms of a dumping stomach are often encountered in nonoperative cases of benign achylia with patulous pylorus. The small intestine becomes rapidly distended, obliterating the normal herring bone pattern of the mucosal relief. In these cases HCL therapy to the point of tolerance has adequately retarded rapid express of food and has eased postprandial discomfort. Alvarez (2) declares and the writer agrees that "The dumping syndrome can be seen in hypersensitive, overly reactive or psychoneurotic persons who have not had any operation on the stomach. In them, it appears to be due to the rapid outpouring of food through a patulous pylorus." Obviously faulty surgery holds no monopoly on the utilization of the term "dumping." Malignant achylia is another instance where rapid gastric clearance occurs and among other abdominal symptoms distension prods the patient to call for medical consultation. The large stoma seems to operate disadvantageously in both types of operation with the noted difference that the simple gastroenterostomy patient is more stomach conscious. In one instance shrinkage of the stomach was marked and, fortunately, the pyloro-duodenal region functioned normally and symptoms of dumping were conspicuously absent. Review of this particular history leads one to question, why was this patient's gastric physiology interfered with? But excuse was found in the date of the operation — in its very early days. Contrast this case with a gastrojejunal stoma that worked as a mere drainage operation with the pylorus

also functioning adequately. A situation of express gastric drainage set in, overloading the small bowel, as betrayed by marked postprandial distress. It was clearly noted that the distance of the site of the anastomotic stoma from the pylorus varied the post-operative clinical picture. The nearer the stoma to the pylorus, the more significantly retarded the course of the meal through the small bowel which, therefore, was not distended. In another case the flow of the opaque medium ran continuously from the esophagus, through the lower pole of the stomach and into the efferent limb of the anastomotic stoma. Only on the prone x-ray films was some of the opaque medium seen going through in a thin stream through the functioning pylorus — the former being a distance away from the pyloric segment. It was no easy task to divorce this patient from his stomach consciousness when he had all the attributes of a floating patient. Granted that there are cases where the surgeon is confronted with insurmountable difficulties in a patient in poor general condition, under such circumstances a simple gastroenterostomy is all that appears rational to perform. However, it must be admitted that when an anastomotic stoma is too large, is placed too high, when there is a long afferent jejunal loop, the patient harbors a post-operative disorder in exchange for a pre-operative disease. Carman and Miller (3) under the caption of "Stomach after Operation" refer to Moynihan's classification of ". . . four varieties of misdirected current, any one of which establishes circulus vitiosus." The writer believes it is here pertinent for review. "1 — Regurgitation of duodenal contents through the pylorus. 2) Escape of fluid from the stomach into the afferent loop. 3) Escape of fluid from the afferent loop into the stomach, most frequent and grave variety. 4) Regurgitation of contents of the efferent loop into the stomach." The "vicious circle" phenomenon should forever be borne in mind in the management of unequivocally diagnosed cases of post-pyloric lesions. The striking and significant portent of duodenal ulcer disease is further emphasized in this small group of patients when it is realized that a post-operative picture might ensue which is as deleterious to the patient's well being as the pre-operative symptomatology. Surgical intervention is warranted only by the occurrence of the orthodox complications of the disease. But where surgery is undebatably indicated, one would incline even from the review of a meager number of cases, to the view that advocates discontinuing the performance of simple gastroenterostomy in cases of sustained hyperchlorhydria and thereby eliminating gastrojejunal ulcer in many instances. Again in this small group with a fair opportunity of a follow-up the occurrence of achlorhydria did not occur in simple gastroenterostomies. Since the important function of partial gastrectomy is that of preventing marginal or jejunal ulcer in patients with duodenal ulcer associated with high gastric secretory values, this should be the operation of choice. A ready aspiration of clear bile post-operatively supplies the need for neutralization of acidity. This factor is brought into play by a short proximal loop which supplies an alkaline bath for the stoma, thus furnishing effective neutralization of acid secretion. This point is to be borne in mind when partial gastrectomy is not available. Where gastric contents were not bile tinged, a long afferent loop was brought into view. Bockus (4) writes, "The advocates of partial gastrectomy, base their claims for superiority of their procedure upon: (1) removal of the large part of the ulcer bearing area, (2) reduction in or complete disappearance of gastric hydrochloric acid, (3) reduced incidence of marginal and jejunal ulcer, (4) fewer recurrences and (5) possibly the removal of a diseased 'gastritic' mucous membrane in some cases." Agreeing with this enumeration, Winkelstein and Berg (5) stated with reference to achlorhydria, ". . . we feel definitely from a very long experience with a large series of surgical cases that it is definitely the sine qua non for the prevention of ulcer recurrences." The post-operative achlorhydria alluded to may be easily corrected by replacement therapy, reinforced by dietary regimen, and much reliance may be placed on a compensatory mechanism such as operates in cases of asymptomatic congenital achylia gastrica.

In conclusion, pitting the illustrative case of simple gastroenterostomy against the more aggressive partial gastrectomy, the superiority of the latter became compelling from a clinical follow-up.

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ABSTRACTS ON NUTRITION

BEAN, C. G., JOHNSON, R. E., KARK, R. M., CONSOLAZIO, C. F., SWEET, H. L., LAUBACH, A., MALONEY, M. A., PITTMAN, W. G. AND DIFFORATE, L. E.: *Survival in the cold.* (United States Armed Forces Med. Jour., 1, 6, 615-628).

During the course of a field test on the nutritional requirements of rations for survival in the cold, a comprehensive study was made on 32 volunteers flown directly from Florida (temperature, +70° F.) to Manitoba, Canada, (temperature, −20° F.) in the dead of winter. Complete metabolic balance studies were made for 12 days during which time 4 groups of 8 men were segregated in separate "survival" areas and ate 1 of 4 different rations. Clear answers were obtained on the balance requirements for calories, water, protein, carbohydrate, fat, sodium, potassium, chloride, calcium and phosphorus. Frequent biochemical, physiologic and hematologic observations suggested that during the first two days of abrupt exposure to cold, unacclimatized soldiers exhibit a general adaptation syndrome, with stimulation of the pituitary-adrenocortical system. It is suggested that similar continued study should include an assessment of the possibility of pre-acclimatizing men by treatment with ACTH.

CREVELD, S. V.: *Nutritional deficiencies in small children of the Netherlands.* (Int. Health Bulletin, League of Red Cross Soc., II, I, 10-14).

Protein and calories appear more important than vitamins in the nutrition of children. Faulty assimilation is responsible for protein inadequacy particularly in celiac disease, which is becoming more and more frequent in Holland. Vitamin A deficiency is rare in Holland in infants under one year of age, but is found in celiac disease especially where too much mineral oil has been employed. Thiamin deficiency is rare in Holland in children over a year old. Riboflavin deficiencies were common in the Java Concentration Camps, where children subsisted on a diet increasingly impoverished in protein, calories and vitamins, so that most of them developed nutritional edema, ariboflavinosis and pellagra in varying degrees of severity. These conditions were frequently aggravated by infectious hepatitis, helminthiasis and tertian malaria. In Holland anemias were commonly found in celiac disease and hypothyroidism. The Plummer-Vinson syndrome often is found among adults but rarely in children.

LINCOLN, M.: *What can happen when diabetics marry.* (Northwest Med., 49, 7, 466-67).

The author refers to the work of Joslin and others who have indicated the high degree of inheritability of diabetes and describes a family in which the father and mother were diabetic. By this marriage there were nine children. Two died of diabetes in childhood. Of the six living, besides Lincoln's patient, all are obese and all are known diabetics except one brother who is a Christian Scientist and refuses to see a doctor, although he is sick. The father did not develop diabetes until middle life and the mother not until her sixties, suggesting that both were relatively mild diabetics. There are 8 grandchildren, none of whom is at present a known diabetic.

SHAW, C. R., BECK, F., PILCHER, H. AND PARKER, J.: *A study of the relation of nutritional status to pulmonary tuberculosis.* (Am. Rev. Tuberculosis, 62, 1 A, 58-66).

187 adults with pulmonary tuberculosis and 118 nontuberculous adults were studied from the standpoint of serum determinations of hemoglobin, vitamins A and C, carotene, alkaline phosphatase, and total protein. Detailed dietary studies were made on 25 patients and on 17 nontuberculous persons. The diets of the tuberculous and non-tuberculous were fairly comparable in all nutrients and food types. Of the 25 patients studied who had no, slight, or moderate symptoms, there was no relation between severity of symptoms and food intake. There was no close correlation between severity of symptoms and diminution of blood levels of all nutrients studied. In severe cases, blood levels of nutrients were greatly reduced. Whether this is due to inadequate food intake or the toxic febrile state, or unique in tuberculosis, must be decided through further studies.

GAISFORD, W. AND SCHOFIELD, S.: *Prolongation of the initial starvation period in premature infants.* (Brit. M. J., June 17, 1950, 1404-1405).

Attention is drawn to the advantages of delaying the first feeding of premature newborn infants till 3 or 4 days after birth. It is a safe procedure and has given excellent results. The actual time of first feeding is determined by the individual infant and is decided by his cry and by progressive diminution of urinary excretion.

BERKMAN, J. M.: *A concept of starvation edema.* (Proc. Staff Meet. Mayo Clin., 25, 11, 265-269).

Starvation edema is stated to be a result of disturbance in the metabolism of sodium chloride and not due to hypoproteinemia. During starvation, the kidney's power of excretion of salt and water is impaired and the occurrence of edema results from consumption of more salt and water than can be excreted. The reason that edema is not a regular feature of the starvation in cases of anorexia nervosa is probably that these individuals drink very little liquid. On treating a patient with anorexia nervosa, the increased calories and fluid result temporarily in a situation in which the imbibed salt and water cannot be handled by the kidney, and this results in a transient edema which soon disappears as the renal excretory power improves. Berkman feels that in the early treatment of anorexia nervosa, transfusions, intravenous infusions of fluids and tube feeding, appear to be dangerous. A diet high in protein and high in calories is all that is needed, for the sodium chloride metabolism is soon corrected through renal recovery.

SPENCE, A. W.: *Discussion on obesity.* (Proc. Roy. Soc. Med., XLIII, 5, 339-342).

Most cases of obesity present no obvious evidence of endocrine disturbance. Livestock may be fattened by castration, but eunuchs may either be tall and lean or fat. Adiposity is not regularly or often associated with hypothyroidism. Obesity associated with adrenal tumors may be due to excessive conversion of protein into glucose by corticosterone, and the subsequent conversion of glucose into fat. Obesity may be caused by hyperinsulinism due to a tumor or to hyperplasia of the islets of Langerhans. Obesity commonly follows pregnancy, due possibly to hyperfunction of the adrenal cortex. *Spence does not think that overeating is responsible for many cases of obesity.* Certain cases of sporadic, familial and racial obesity may be due to an upset in a weight-regulating mechanism in the hypothalamus. We know very little concerning the causation of obesity. The use of pituitary extracts in all cases of obesity is valueless. Thyroid extract helps only where hypothyroidism is causal. Reducing diets should be supplemented with vitamins A and D. It is a remarkable fact that sometimes weight is lost more rapidly when the patient is treated at rest in bed than when up and about.

GYRTZEN, O.: *Diet in the treatment of acute hepatitis.* (Brit. Med. J., May 20, 1950, 1166-68).

In 3 parallel series of 97, 56 and 54 cases of acute epidemic hepatitis, diets of protein, carbohydrate and fat, respectively, were given with a balanced basic diet, the caloric content being maintained at about 3000. No statistical difference as regards duration of treatment or the time required for blood and urine tests to become normal was found. Therefore, a considerable measure of freedom may be used in the composition of the diet, since an increase of protein, or of fat, or of carbohydrate, had no effect on the course of the illness.

ALLEN, F. M.: *Hypertension and nutrition.* (Nutrition Reviews, Sept. '49, 7, 9, 257-261).

This article can scarcely be reviewed except critically. Allen, the first proponent of "saltless" diet in essential hypertension in America, made his first claims to successful treatment in the early 20's but for some reason his work was not generally accepted, possibly, as he says, because salt was not sufficiently excluded, nor the diet continued long enough. He believes that *essential* hypertension (not nephritic hypertension) is a specific disease due to the patient's susceptibility to sodium chloride and can be cured in most cases by the salt-free diet (less than 1 gram NaCl per day) or even prevented by a low-salt diet. Kempner's work brought the whole matter up again but certainly has not persuaded everyone of the value of the low salt diet. Allen correctly quotes Selve's work which indicates that hypertension may be produced by corticosterones with a sodium atom in them, but he denies that high protein intake has anything to do with hypertension, although Selve's theory of the alarm reaction actually postulates a high blood protein level.

Allen declares that low salt diet prevents congestive cardiac failure, retinitis, angina and uremia. He admits, however, that salt is merely the principal, not the sole influential factor, but he does not appear to elaborate on the "other" factors. Such a tight case for complete control of essential hypertension is presented that too great a strain is placed upon belief. Acceptance naturally could only come from duplication of his results, yet Kempner's good results have not been widely repeated. He makes too little mention of the collapse symptoms which may follow too restricted a salt intake. Obviously, we must now await further work on human subjects before Allen's claims can very well be accepted, and this may require twenty years or more.

HOLMES, A.: *Comparison of the stability of reduced ascorbic acid in raw and pasteurized milk.* Am. J. Dis. Child. Dec. 1949, 78, 6, 899-902.

Pooled herd milk was pasteurized by the holding method, with light excluded, at 143°F. for 30 minutes. Pasteurization caused an average loss of 12 percent of the reduced ascorbic acid. During 5 days of storage, the raw milk lost 64 per cent of its reduced ascorbic acid and the pasteurized milk lost 77 per cent.

HOWE, P. E.: *Nutrition in public health in Japan.* (U. S. Armed Forces M. J., 1, 6, 694-702).

Since nutritional inadequacies are likely to result in civil unrest and dissatisfaction prejudicial to the occupation, the

Supreme Commander Allied Powers, working through the Ministry of Welfare, carefully investigated nutritional deaths and caused nutrition surveys to be made regularly. Most frequently there are no symptoms or signs in early deficiencies. It was found that natural selection of foods often results in adequate diets, so that indigenous diets were not interfered with unless urgent. Japan has legislated to regulate the milling of rice so as to retain antiberiberi factors in grain. Special food supplements are permitted for such special groups as hospital inmates, pregnant women and children. Anemia in urban sections was found in 10.1 percent of those examined. The loss of the knee jerk occurs in 10.2 percent in urban areas each year in May and August, due probably to the deterioration of the rice with loss of thiamine on storage. The same remarks apply to bradycardia.

EDITORIAL

THE TREATMENT OF PERNICIOUS ANEMIA

It now seems certain that vitamin B_{12} is capable of doing all that refined liver extract can do for pernicious anemia, both hematologically and neurologically. The fractions designated vitamin B_{12a} and vitamin B_{12b} have both been crystallized from liver and are clinically active. Vitamin B_{12a}, produced by catalytic hydrogenation from B_{12} is thought to be identical with B_{12b} and it also is active clinically. So far as we know at present, only B_{12} is required in the treatment of pernicious anemia.

The fact that folic acid, in many cases of pernicious anemia, has produced fair to good blood remissions would logically suggest that it is needed for hematopoiesis, for were it not essential, it could not be expected to produce blood improvement. Yet, since almost all cases of Addisonian anemia enjoy excellent blood remissions from vitamin B_{12} alone, and particularly since cases maintained on folic acid alone have frequently suffered sudden neurological damage even with their blood counts at a good level, there has been a tendency to avoid the use of folic acid in treatment of this disease.

A case reported by Ungley is perhaps enlightening in this connection. The patient, a man aged 55, had a very poor response to vitamin B_{12} alone, but made excellent progress when small amounts of folic acid were added to the treatment. It may well be that one cause for the occasionally observed failure of B_{12} is a lack of folic acid. If both folic acid and vitamin B_{12} are needed for hematopoiesis in pernicious anemia, then as Ungley suggests, we may have an explanation of the neurological relapses in patients treated solely with folic acid, viz., that the folic acid uses up all the remaining traces of vitamin B_{12} in the body, so that no protection remains for the nervous tissues. Obviously, in the exceptional case, who responds poorly to vitamin B_{12}, there can be no harm in giving small doses of folic acid, making sure that the folic acid is "covered" by adequate or even generous doses of vitamin B_{12}. In Ungley's case, only 15 mg., in all, of folic acid was required to turn failure into success.

A common cause for failure in treatment is insufficient dosage of the "red vitamin" (B_{12}). There is no standard dose and each case must be treated according to its own requirements. Blood remissions may be started on small doses of vitamin B_{12} but in cases presenting spinal cord damage, large doses (e.g. 30 micrograms) ought to be employed daily for at least 2 or 3 weeks or until the neurological manifestations abate. For maintenance, trial and error methods are required to establish dosage, but it should be borne in mind that giving excessive amounts of vitamin B_{12} does no harm. (The use of 900 micrograms daily for 7 weeks has produced no toxic or unpleasant symptoms).

Perhaps faulty *storage* of vitamin B_{12} may play a part in certain cases proving difficult to maintain. Very little is known for certain about the storage of vitamin B_{12} but the liver is assumed to represent the chief site of storage. It is possible that the bile itself in its physiological circuit from liver to intestine and back to liver, may be a site of storage. Ox bile injections were found to produce reticulocyte responses in some cases of pernicious anemia. The writer once saw a beginning remission halted suddenly by a large dose of saturated magnesium sulfate solution employed for gallbladder drainage. Thus far the use of "tagged" vitamin B_{12}, labelled with radio-active cobalt or phosphorus, has not been found possible, so that knowledge as to the *site of action* and *site of storage* of vitamin B_{12} must wait further studies in this direction. At the present moment, where faulty storage is suspected, resort should be had to the use of extremely large doses of the vitamin for a time at least. Bortz recently reported that a single dose of 1,000 micrograms was sufficient to produce a remission and maintain the patient for 12 weeks.

Fortunately, most cases of pernicious anemia can be adequately maintained *for years* by the use of vitamin B_{12} alone. Where iron deficiency exists this should be made good by intramuscular injections of iron and ammonium citrate solution, and the occasional case may require small doses of folic acid, as above stated.

The greatly increased incidence of gastric cancer in patients with pernicious anemia since the advent of liver therapy in 1927 is still unexplained. The increased life span of the patient may permit progressive changes in the gastric mucosa to take place, leading to malignant mutation. Liver extract itself may contain a carcinogenic substance effective in approximately 10 per cent of the surviving patients. It will be of great interest to find out whether this 10 per cent incidence of gastric carcinoma drops to pre-liver levels through the use of crystalline vitamin B_{12}.

The most "logical" form of treatment for pernicious anemia is the dried gastric mucosa of the hog (Ventriculin), inasmuch as it supplies the missing link—the intrinsic factor of Castle, responsible for the genesis of the disease.

Beaumont S. Cornell, M.D.

BOOK REVIEWS

CLINIC AND THERAPY OF MASSIVE GASTRO-INTESTINAL BLEEDING. Nicola Markoff, M. D., 135 pages with 30 illustrations and 1 color plate. Hans Huber, Berne, 1950.

The very well known Swiss author deals chiefly with massive hemorrhage from gastric and duodenal ulcers. The international literature is reviewed concisely and case reports presented. Markoff believes that 90 per cent of cases of gastric bleeding can be adequately treated medically. Early admission to hospital and treatment by blood transfusion is advised. As soon as shock has passed the Meulengracht regime is commenced. One is surprised to read the list of foods used, which are apparently well tolerated in Switzerland, but which would hardly be prescribed in America. Examples are cauliflower, beets and bratwurst. Markoff follows the current tendency noted everywhere to reserve surgery especially for grave cases in elderly persons. The book is highly recommended to all physicians interested in the ulcer problems.

Franz J. Lust, M. D.

THE LIVER. Kasper Blond, M. D. and David Haler, M. B. 268 pages. The Williams and Wilkins Company, Baltimore, 1950, $5.00.

This is a very interesting book, which in spite of its theoretical and iconoclastic flavor, indicates that two doctors have been doing a lot of orginal thinking, which may or may not serve finally to put the *quietus* on cellular pathology and the memory of Virchow. The authors evidently almost believe that liver damage is responsible for all the diseases that exist. For example, they state,—"It is our opinion that all abdominal disorders originate from liver damage." On the basis of increased portal venous pressure they have attempted to rear a master cause,—even for the explanation of appendicitis, hypertension and arteriosclerosis. Angina pectoris belongs to the syndrome of portal back pressure too. The book gives notice that two thinkers are loose in medicine, and their arguments are devilishly clever. Why, O why, did God give us livers? Perhaps someday someone will learn how to do a successful hepatectomy. Seriously however, Blond and Haler ought to be read by the fearless and by those who love scientific novelty.

SCIENTIFIC PRINCIPLES IN NURSING. M. Esther McClain, R. N., B. S., M. S., 410 pages. The C V. Mosby Company, St. Louis, 1950.

No matter how proficient a nurse may be, she will be still more proficient as a result of carefully studying this book. The author has gone to special pains to emphasize the importance of the patient's mental attitudes and, at the end of each chapter, suggests definite information which the nurse ought to give the patient with respect to whatever procedure may be carried out. For example, since x-ray is used in cancer therapy, many patients think that the use of the x-ray indicates that they are suffering from cancer, whereas it may be in use purely for diagnostic purpose. Many details usually found in books on nursing are purposely omitted in order to serve the function of presenting the calling in its broadest aspects. Considerable attention is directed to the nurse herself,—her health, her appearance and particularly her ability to cooperate with her associates and give her patient intelligent and sympathetic understanding. Each chapter contains terminally "exercises" or questions as well as a succinct summary.

The scientific meaning, as well as the techniques of the various procedures demanded of a trained nurse are skilfully described. Thirty pages of references and a good index are included. Since this text appears to cover nursing in a manner different from the majority, it should possibly be placed in the hands of every student nurse.

THE BIOCHEMISTRY OF B VITAMINS. Roger J. Williams, Robert E. Eakin, Ernest Beerstecher, Jr., and William Shive. 741 pages. Reinhold Publishing Corp., New York, 1950, $10.00.

The amount of pertinent material herein presented with respect to the constitution and physiological effects of the various B vitamins represents a monumental task. The authors have attempted to write a book which would be readable and understandable by persons engaged in related or different scientific fields. Considerable attention is given to the theory of structural analogues and antagonistic substances (anti-metabolites). The book is of primary interest to medical specialists, research workers, biochemists, nutritionists, pharmacologists and food technologists. It is very highly recommended.

THE ESOPHAGUS AND PHARYNX IN ACTION. William Lerche, M. D., 222 pages, Charles C. Thomas, Springfield, Ill., 1950, $5.50.

This profusely illustrated text reports an original anatomical investigation by the author, of many esophagi removed from persons dying of various diseases and is of particular value in showing a double closing mechanism between the stomach and esophagus, namely, the constrictor cardiae and the inferior esophageal sphincter. With the discovery of the mechanism of the components in the gastro-esophageal *segment of expulsion*, and the modus operandi of this segment as a unit in coordination with the stylopharyngo-palatino-esophageal muscle apparatus, the operation of the complicated machinery in the acts of regurgitation and deglutition becomes clear. This appears to be a highly scientific and classical contribution to a difficult series of problems in gastroenterology.

CELL PHYSIOLOGY AND PHARMACOLOGY. J. F. Danielli, Ph. D., D. Sc., 156 pages. Elsevier Publishing Co., Inc., New York, 1950, $3.00.

This fascinating volume provides even the inexpert with a working knowledge of the individual cell, particularly from the angle of the action of drugs. Physical chemistry, surface membrane phenomena, physiology of the genes, the reaction of cytoplasm to foreign bodies and much more information concerning the intrinsic behavior of intracellular enzyme systems lay the foundation upon which the actual explanation of the drug effects must be built. Obviously, all this represents an ultra-application of pharmacology, and, while actual knowledge of the cell's physiology is in its infancy, reading the book helps one to visualize, in a new way, not only the vast potentialities which lie before us in the understanding of life but especially, the ultimate *modus operandi* of therapeutic agents. It is most highly recommended.

GENERAL ABSTRACTS

BRANDBERG, RUDOLF: *Mortality and causes of death in cholelithiasis.* Nordisk Medisin, 1950, 43, 590.

For the operative mortality of cholelithiasis with its complications the following data respecting the disease are of fundamental importance. An appreciable incidence of biliary calculus begins at the age of 16-25 in females, and during the following decade in males. Concretion formation then continues to increase with mounting age. In the younger age groups women show a considerably higher incidence of gall stones than men, but subsequently the incidence rises faster in men than in women, so that the discrepancy between the sexes declines with increasing age. Both the incidence and the severity of the cholecystitis increase with rising age. Men are relatively more often and more severely attacked by cholecystitis than women. Expressed in percentages choledocholithiasis occurs with the same frequency in both sexes.

A high incidence of this disease does not appear in women until their 35th year and in men until their 45th year, the incidence subsequently remaining fairly constant. The above circumstances explain why the mortality of operations for gallstones remains low up to the age of 55 years—in the present series—1. 5.2 percent—thereafter increasing rapidly, and more so in men than in women—to the present series to 21 and 9 percent respectively. The increase is due to the coincidence of two unfavourable factors, namely old age attended, for various reasons, by a reduced power of resistance to operative measures, and a higher incidence of malignant forms of the disease. Computed on the whole series of 1255 cases (1160 cases of cholelithiasis with and without complications, and 95 of cholecystitis without stones), the mortality is 5.3 percent. In men the rate is 10 percent, in women 4 per cent. The higher mortality in men is due to the fact that a greater group of men than women belong to the higher age-groups, in which the incidence of severe cases is highest and, moreover, is higher for men than for women.

With the diagnostic and therapeutic advances made during the last few decades the mortality associated with the bile-duct surgery can undoubtedly be brought down further, although, as is evident from the foregoing data, there will always remain a considerable mortality in the higher age-groups. The possibility of avoiding by earlier operation the severe morbid forms and the major operative risks accompanying senescence is rather limited. For the majority of these patients, and especially those showing the most malignant cases, have a short course.

O. W. Huseby, Oslo.

HUSCHNESS, FRITZ: *The diagnosis of nervous peptic intestinal disturbances.* Nordisk Medisin, 1950, 43, 391.

The diagnosis of nervous peptic-intestinal disturbances is primary and should not be made by exclusion. These disturbances are relatively mild in clinical pictures of a distinctive type, —the stigmatized neurosis (a minority). The diagnosis may be very difficult in less characteristic clinical pictures of non-stigmatized neurosis and psychopathias. In order to evaluate and classify the nervous peptic-intestinal disturbances it is necessary to have an accurate case history, detailed knowledge of the symptomatology of organic peptic-intestinal diseases and a proper classification of the psychic disturbances. In cyclothymia, frequent in the pyenic type, the differential diagnosis is chiefly concerned with ulcer disease. In the asthenic (leptosomatic) type, the differential diagnostic alternatives are gastritis chronica vulgaris, enteritis, colitis simplex, spastic constipation and atypical cholecystopathy. It is necessary to distinguish the following from neurotic and psychic disturbances: functional disturbances due to irradiation of autonomic reflexes, to hormonal disturbances, physical asthenia without psycho-asthenia, and dyskinesia.

O. W. Huseby, Oslo.

PLOMANN, LENNART: *Polyposis coli.* Nordisk Medisin, 1950 43, 506.

Following definition of the nature of polyposis coli, a brief description is given of the clinical syndrome. Emphasis is laid on the tendency to malignancy and the heredity, and the treatment is discussed. He concludes with a report on a fulminant case, the heredity being illustrated by a family history showing the disease in at least eight of sixteen persons.

O. W. Huseby, Oslo.

QUIDSTAD, IVAR: *Spontaneous perforation of the large bowel.* Nordisk Medisin, 1950, 43:504.

Report on a case of spontaneous perforation of the large bowel (transverse colon) in a new-born male infant. The perforation was assumed to have occurred between the 4th and 5th day of delivery. The child died on the 6th day. The clinical course, as well as the gross post mortem findings were consistent with those previously reported. Microscopy revealed a defect in the muscular layer at one side of the perforation. This may possibly explain the pathogenesis as a congenital anomaly, since a relatively slight increase in the intra-intestinal pressure alone might cause a perforation.

O. W. Huseby, Oslo.

FJORTAFT-PETTERSEN, V., AND HOLSTMANN, P.: *The significance of gastric motility in nausea.* Nordisk Medisin, 1950, 43, 491.

Physiopathologic problems in nausea are reviewed. The present investigations showed that: 1) Nausea, either of spontaneous origin or induced by injection of apomorphine or by caloric vestibular stimulation, is associated with inhibition of the contractions of the stomach. This inhibition starts before and ends later than the nausea. 2) Inhibition of gastric contractions may appear spontaneously or e.g. following injection of atropine without nausea being felt. 3) The inhibition of gastric motility is probably not the cause of nausea. 4) No correlation seems to exist between the effect of various drugs on nausea and on gastric motility. 5) Recording the motor function of the stomach cannot be used as a test of the effect of a drug on nausea.

O. W. Huseby, Oslo.

STRANG, C. AND SPENCER, I. O. B.: *Factors associated with perforation in peptic ulcer.* (Brit. Med. J., Apr. 15, 1950, 873-876).

In studying 189 consecutive cases of perforated peptic ulcer admitted to the Royal Victoria Infirmary, Newcastle-upon-Tyne, during the period of a year, it was generally confirmed that the perforation itself always was unpredictable. A slight majority had pain or discomfort during the three days before perforation. There were fewer perforations in the autumn than in other seasons. Perforations occurred more frequently between noon and midnight than in the morning hours. In men, ruptured duodenal ulcer was four times as common as ruptured gastric ulcer, but in women perforated gastric ulcer was twice as common as perforated duodenal ulcer.

COPPLESON, V. M.: *The diagnosis and management of carcinoma of the colon and rectum.* (Med. J. Australia, March 18, 1950, 353-356).

The diagnosis of colonic and rectal cancer leaves much to be desired, since one growth out of every four is inoperable when discovered. Patients present themselves too late. Radiography can diagnose only advanced lesions. Sixty percent of cancers are within reach from the anus by finger or sigmoidoscope. Primary resection should be carried out always on the right side and, when possible, on the left.

LING, C. C. AND KOO, S. N.: *Multiple leiomyosarcomata of the stomach.* (Chinese Med. J., 66, 594-596).

Prior to the case presented by the authors, only 368 authentic instances of gastric leiomyosarcomas had been reported. The present case was successfully treated by subtotal gastrectomy. Symptoms and signs are not diagnostic, but bleeding is the most important and sometimes the sole clinical manifestation. Obstruction ranks second.

SNORF, L. D.: *Clinical experiences with ulcerative colitis.* (Miss. Valley Med. J., 72, 3, 64-68).

Snorf admits ignorance of the etiology of chronic ulcerative colitis, but notes that infections, infestations, allergic reactions and emotional conflicts may be associated with its onset. In 75 percent of cases emotional upset plays a tremendous role. In treatment he uses a low residue diet and no milk. He feels that large intravenous doses of ascorbic acid (1 to 2 grams daily) help to control bleeding. Anemia is looked for and treated by iron. In violently ill patients, transfusions, bed rest and high protein intake are necessary. Sulfonamides and antibiotics do no good. Ileostomy should be performed if necessary. He has not had convincing results with defatted extract of hog intestine nor with "medical ileostomy" by the Miller-Abbott tube.

LONG, J. W., MAYO, C. W., DOCKERTY, M. B. AND JUDD, E. S., JR.: *Recurrent versus new and independent carcinomas of the colon and rectum.* (Proc. Staff Meet. Mayo Clin., 25, 8, 169-178).

There are three ways by which cancers may reappear in the vicinity of an anastomotic site after removal from the large bowel of an original growth of the same type. First, and commonest, is through a continuation of the growth of malignant tissue which the surgeon inadvertently left behind. (The prognosis in this group is poor). Second, a cancer may reappear by malignant transformation of a neighboring polyp. Third, there may develop fresh cancerous changes from *predisposed epithelium* in the region of the original tumor. Thus a zone of the colon may be "predestined" to evolve fresh cancers.

AMER. JOUR. DIG. DIS.

Teitelbaum, M. D. and Arenson, Nathan: *Recurrent small intestinal intussusception in children.* Am. J. Roentgen. & Rad. Th. 63, 1, 80, Jan. 1950.

Five cases of small intestinal intussusception are described. This condition in young children is more frequent than is commonly believed. It is presumably a manifestation of neuromuscular dysfunction and, in some instances, may be an allergic response. The intussusception, which is transient, recurrent and usually involves multiple segments of the small intestine, produces rather constantly, intermittent abdominal pain with nausea and sometimes vomiting. The symptoms may be present for months or years and the single attacks may be very severe. However, there is no strangulation or obstruction. No tumor masses can be felt, and there is no bleeding from the bowel.

Franz J. Lust.

Mangold, Otto and V. Woellwarth, Carl: *Situs inversus of the intestinal tract, heart and nucleus habenulae.* Aerztl. Forschung 3, 8, 206, April 26, 1950.

Physiological experiments on development by Spemann and others have led to the conclusion that left-sided defects in the earliest stages of embryonal development may induce a reflected image or inversion of the intestines. Extensive experiments on defects in the germ of amphibians have brought the confirmation and completion of this theory. Also the inversion of the situs by the rotation of a piece of the medullar plate and the roof of the primary gut, could be explained by the defect theory. The abundance of material allows one to compute a measure for the correlation of the position of the different asymmetrical organs. The habenula of the middle brain, also asymetrically formed in amphibians, participated in the inversion of the gut, although its origin is not concerned in the operation. This leads to the conclusion that the operation takes effect in an early stage of determination, extending from the center of organization through the whole germ, and probably causing the asymmetry of all organs.

Franz J. Lust.

Schliephake, E. and Sattler, Ch.: *The behaviour of the endocrine system in patients with gastric diseases, determined by short wave functional tests. (Das Verhalten des endokrinen Systems bei Magenkranken, festgestellt mit Kurzwellen-Funktionspruefungen).* Neue Medizinsche Welt 1, 9, 300, March 4, 1950.

The authors use ultra short waves for their experiments. It is their opinion that not only heat is generated by this method, but that the cell membranes are influenced too. The treatment with short waves was applied to the region of the hypophysis, the epigastrium, and the genitals. Following this treatment, the blood sugar was determined every 15 minutes. In healthy persons, the blood sugar curve has a certain regular outline. In patients with stomach disorders, especially in those with gastric or duodenal ulcers, the blood sugar curves have a definite changed outline compared to normal. To the authors, this is proof that in these gastric conditions, a disturbance is present in the endocrine system, in which the hypophysis and the genital organs are involved.

Franz J. Lust.

Palazzo, William L. and Schulz, Milford D.: *Spindle-cell tumors of the gastro-intestinal tract.* Radiology 51, 6, 779, December 1948.

Spindle cell tumors of the gastro-intestinal tract were found in 0.67% of 12,000 necropsies and in 1.2% of 5,313 surgical records at the Massachusetts General Hospital. Both benign and malignant varieties occurred with increasing frequency as age progressed. Of the total 140 spindle-cell tumors, 9% were located in the esophagus, 65% in the stomach, 17% in the small intestine, and 9% in the colon. Spindle cell tumors accounted for 2.3% of all tumors surgically removed from the esophagus in the past 16 years, for 5% of those in the stomach, for 7% of those in the small intestine, and for 0.2% of those in the colon. Of those spindle-cell tumors found in the esophagus, 33% were malignant, in the stomach, 36% were malignant, and 54% of the patients bearing the tumors remained well and free of disease for an average of 8 years. Recurrence or metastasis, if present, was evident within 4 years. Metastasis to the liver and lymph nodes occurred in 33% of the malignant gastric tumors. In the small bowel 77% were malignant; none of the patients remained free of disease for longer than 3 years. 86% of the colon tumors were malignant, only one patient of this group is alive and no sign of recurrence for 5 years. —There are no safe criteria by which the benignity of such a tumor may be recognized with certainty.

Franz J. Lust.

Davis, Frank W. Jr., M. D.: *Amebiasis: Experience in Johns Hopkins Hospital, 1936-46.* Am. J. Med. Sc., May, 1949, vol. 217, No. 5.

In this 10 year survey 205 proven cases are analyzed and the incidence of the various symptoms, physical and laboratory findings, and complications, were found to approximate those generally accepted.

Follow-up studies revealed interesting findings. In 25% of all cases moderate to severe gastro-intestinal symptoms persisted following adequate therapy, in the absence of demonstrable parasites. The syndromes included "spastic colon," bouts of diarrhea, chronic diarrhea, and typical chronic ulcerative colitis. 12 of the 205 cases progressed to typical ulcerative colitis and in 9 out of these 12 amebic pathogenesis for the ulcerative colitis is strongly suggested, although the mechanism of the relationship is unknown.

Nathan Lane, Jr.

Holt, John F., Lyons, Richard H., Nelgh, Rosalie B., Moe, Gordon K., Hodges, Fred G.: *X-ray signs of altered alimentary function following autonomic blockade with tetraethylammonium.* Radiology 49, 5, 603, November 1947.

Tetraethylammonium is a simple organic compound which possesses a recently recognized property that is unique among known pharmaceutical agents. Parentally administered the drug appears to block the transmission of impulses through the autonomic ganglia—both sympathetic and parasympathetic. Preliminary roentgenological observations indicate that the drug produces diminution of gastro-intestinal tone and causes virtually complete cessation of motility in the small bowel. In many instances, however, movements of the small intestinal mucosal folds are completely stopped for relatively long periods of time. This is in contradistinction to the action of atropine and adrenalin, both of which produce some decrease in motility but neither of which has any appreciable effect on mucosal movements. Artificial paralysis of autonomic ganglia does not consistently produce all of the classical roentgenological features of "disordered motor function" of the small intestine as seen in various nutritional disorders, gastro-intestinal allergy, diabetic neuropathy, and other conditions.

Although the therapeutic value of tetraethylammonium at present is distinctly limited, further study of its properties may find it a place in medical management.

Franz J. Lust.

Kabe, E. F. and Dunphy, D. L.: *Agglutinating substances for homologous coliform organisms.* Am. J. Dis. Child. 1949, 78, 5, 717-727.

Substances capable of agglutinating coliform organisms obtained from babies' intestinal tracts occurred in the serum of 76.4 per cent of 17 healthy infants and in 80 per cent of 20 infants with idiopathic diarrhea. Similar substances capable of agglutinating homologous coliform organisms were found in stools of infants with epidemic diarrhea of the new-born and in infants with sporadic diarrhea in 75 per cent of the 20 babies examined, —a greater incidence than in the feces of healthy infants. Fecal agglutinating substances probably result from a transudation of extracellular fluid across the intestinal wall. The investigation did not elucidate the role of the coliform organisms in idiopathic infantile diarrhea.

Robinson, J. C., James, G. W. and Kabe, E. M.: *The effects of oral therapy with cobaltous chloride on the blood of patients suffering with chronic infections.* New England Jour. Med., 240, 19, 749-753.

Nine patients who were anemic and suffering from prolonged infections were treated for from 2 to 11 weeks by the daily oral administration of cobaltous chloride in doses of from 20 to 60 mgm. per day. In all patients, beginning usually on the 4th or 5th day, reticulocyte responses were obtained, reaching their maximum (never over 5 per cent) between the 6th and 10th day, but with reticulocytosis continuing through the period of treatment. *In all cases the anemia was overcome.* The blood volume increased due to the increase in the mass of circulating red blood cells but the plasma volume changed but slightly. As yet the authors have no explanation for the results obtained. Toxic symptoms were absent, although in two cases there was slight anorexia.

EVANS, W. A.: *Obstructions of the alimentary tract in infancy.* (Radiology, July 1948, Vol. 51, No. 1, 23-35).

By observation of common obstructive lesions in 400 infants during the past 7 years at Children's Hospital of Michigan, it was found that hypertrophic pyloric stenosis constituted 50 percent of the total. Intussusception accounted for 20 percent, congenital bands 2 percent and volvulus 2 percent. Atresias and meconium ileus had their highest incidence in the first week of life, pyloric stenosis in the fifth week and intussusception from the 4th to 8th month.

CUNNINGHAM, G. J.: *Intestinal lesions in malignant hypertension.* (Brit. Med. J., June 5, 1948, 1075-1077).

A case of malignant hypertension is reported, in which, terminally, gastro-intestinal ulceration and hemorrhage occurred. A peritonitis also developed though no perforation in this case could be demonstrated. The author shows that while the effects of hypertension on the heart and kidneys are well known, it is not so well known that the gastro-intestinal tract may be seriously involved in this vascular disease, particularly in cases of malignant hypertension.

KIRSNER, J. B. AND PALMER, W. L.: *The present management of peptic ulcer.* (Ill. Med. J., Dec., 1948, Vol. 94, No. 6, 357-361).

The fundamentals of ulcer therapy today are essentially the same as those emphasized by Sippy and others more than 30 years ago. There is still no procedure, medical or surgical, with the exception of total gastrectomy, that regularly produces complete and permanent anacidity; hence, there is no procedure which regularly leads to cure of the disease. The majority of cases, however, are benefitted by a program of physical rest, relief from emotional stress, and continued neutralization or inhibition of the gastric acidity. The most important principle of medical treatment is the "cure of the man as well as his stomach." Surgical treatment is indicated in 10 to 15 per cent of cases for complications of peptic ulcer. Partial resection is reserved for those gastric ulcers in which the possibility of cancer cannot be excluded. Transabdominal vagotomy and posterior gastroenterostomy are indicated chiefly in stenosing duodenal ulcers. Jejunal ulcer is best treated by vagotomy alone.

VAUGHN, A. M.: *Vagotomy in the treatment of gastro-intestinal ulceration.* (Ill. Med. J., June 1949, Vol. 95, No. 6, 343-349).

Vaughn believes it will require the elapse of fifteen years to give us a good perspective of the various results of vagotomy, although he favors the procedure because it possesses a sound physiological background.

MULLEN, B. P.: *Surgery of the pancreas.* (Northwest Med., Feb. 1948, Vol. 47, No. 2, 108-111).

The author covers pancreatic lithiasis, cysts, adenoma of the islets of Langerhans, and cancer. The insulin requirements of the totally depancreatized man are less than for most diabetics. It is believed there may be an insulin antagonist present which is removed with the pancreas. Insulin sensitivity may develop in cases of total pancreatectomy.

OSIUS, E. A.: *Appendicitis in the tuberculous patient.* (Harper Hosp. Bull., July-Aug. 1948, Vol. 6, No. 4, 108-110).

The diagnosis of appendicitis in the tubercular patient is sometimes difficult owing to the protean manifestations of both pulmonary and abdominal T. B. Tuberculous involvement of the appendix has a poor prognostic significance and is often overlooked.

MIKKELSON, O.: *Treatment and prognosis of carcinoma of the rectum.* (Nordisk Med., Dec. 24, 1948, Vol. 40, No. 52, 2401-2403).

Surgery is considered the only radical treatment in cases of operable cancer of the rectum. The operative measures in common use consist in colostomy and perineal resection, or combined abdomino-perineal resection in one or two stages. Local excision may come into use in cases with a small, localized growth or in patients in the older age groups. The combined abdomino-perineal resection should be preferred in the majority of patients. In several clinics the less hazardous sacral amputation of the rectum, with or without preceding colostomy, is the operation preferred. The various disadvantages of this operation, in the author's opinion, make it inadvisable except in a limited number of cases, partly because of resulting and long-standing fistulae. In 115 abdomino-perineal resections done in a 5 year period up till 1942, 12 died in the hospital and 103 were discharged. Of the latter, 53 per cent lived 5 years or more, and 48 patients died within a 5 year period. In 7 of these patients, autopsy failed to demonstrate any recurrent cancer, and 9 others did not present any clinical evidence of recurrence. Thus the percentage of "cures" is nearly 60. The resectability in the material from the years prior to 1942 was 46 per cent. During the past few years the corresponding figure has been 74 per cent.

BACON, H. E. AND HERING, H. C.: *Cancer of the rectum and pelvic colon.* (J. Ark. Med. Soc., Feb. 1949, Vol. 45, No. 9, 170-173).

All lesions of the middle and upper sigmoid are resected by immediate establishment of continuity or by the Mikulicz-Rankin exteriorization method. All lesions of the lower third of the sigmoid, rectosigmoid, and ampullary portion of the rectum by an abdominoperineal proctosigmoidectomy, without colostomy and with preservation of the sphincter musculature. All lesions of the low rectum and anal canal by an abdominoperineal excision by the classical method described by Miles.

NEW COMPOUND RELIEVES MANY DROPSY PATIENTS

A new compound, found in preliminary trials to be of value in relief of many patients with edema and dropsy, has been developed at the Sterling-Winthrop Research Institute. So far the compound is known only by its laboratory number WIN 3000.

The compound resulted from research on ion exchange, which has been in progress at the Institute for some years, according to Dr. Maurice L. Tainter, director. Dr. Tainter stated that the new product will soon be made widely available for further clinical evaluation and therapeutic use in appropriate clinical cases.

First information on the ion exchange research was made public at the Fall meeting of the American Chemical Society, Chicago, Sept. 5, in a paper by Dr. Tainter and Doctors Evan W. McChesney and Frederick C. Nachod of the Institute.

This paper reported that ion exchange resins, afford relief to patients suffering from heart conditions, high blood pressure and similar complaints requiring salt-free diets. The same resins also help remove excess stomach acids to relieve pain in gastric ulcers.

Ion exchange resins were defined as "insoluble materials which have the property of exchanging one chemical entity (an ion) for another. Where a specific ion is deleterious or objectionable in certain diseases or conditions, there is the possibility of using a resin to substitute other ions for the one objectionable."

Swallowed before meals these resins remove most of the sodium from salted foods which may be bad in some heart conditions. Too much sodium in the body leads to watery swellings, or dropsy. The resins must be used only under a doctor's direction, the paper emphasized.

The paper reported extensive trials had been made on both animals and human patients with "encouraging results," following an original suggestion published by Dr. William Dock of Long Island University in 1946. Dr. Dock suggested that the resins would allow the consumption of a fairly normal diet while reducing the danger of edema.

Dr. H. L. Segal and others of the University of Rochester have suggested the feeding of ion exchange resins to relieve the symptoms of gastric ulcer. Ulcer patients experience distress as a result of excessive acid secretion by the stomach and the action of this acid on an ulcerated area.

The study of patients suffering from gastric ulcer shows that they can easily take amounts of resin necessary to neutralize the gastric acidity and give relief, the paper said. Small doses are taken several times a day, perhaps as often as 4 to 8 times. It has been found that this treatment will usually render them pain-free in about a week and that they will remain so on prescribed diets with frequent doses of resin.

FOR THE AGED

Formation of the first pharmaceutical concern to specialize in the production and distribution of ethical drugs, developed to meet health problems of the aged and aging, has been announced by E. Walton Bobst. This firm, Bobst Pharmacal Co., Inc. of which Mr. Bobst is president, has opened offices and laboratories at 305 E. 47th St., N. Y. C. West coast offices have been simultaneously opened at 305 N. Bedford, Beverly Hills, (Cal.) under the direction of John A Roosevelt, Executive Vice-President in charge of sales. Mr. Roosevelt is also associated with the Lee Pharmacal Company.

Mr. Bobst, recently with William R. Warner, and before that with Hoffmann-La Roche, Inc. is the son of Elmer H. Bobst, President of Warner-Hudnut, Inc., who is also active in the field of geriatrics. Other officers of the company will be named shortly.

It is planned to launch six new products in mid-November. These pharmaceuticals, developed as a result of several years of specialized research are: Acetycol, to provide pain relief and increase motion-range in the arthritides; Theo-line for myocardial stimulation, vasodilation and diureses; Theocholin for hypertension; Ther-a-gel for the management of digestive disorders; Cellusena, a laxative for the aging patient; and Vimone, a balanced hormonal-vitamin metabolic stimulant. These will be prescription items sold generally through drug stores. This company will confine itself to working with the medical and pharmaceutical professions.

The first territories to be opened by the new firm are metropolitan New York, Los Angeles and San Francisco. In forming this new concern Mr. Bobst felt that the acceleration of the trends towards specialization in medical science called for corresponding concentration in pharmaceutical production to meet specific health needs.

"The problem of the aged and aging has become increasingly important since the proportion of the aged to the rest of the population has taken a sharp rise. Over 12,000,000 people in this country are over 65, and surveys indicate that this figure will increase in succeeding years. The necessity of keeping these people healthy and working has been emphasized at the President's convention for the aged, and in many other ways. This question has important bearing on the whole problem of man-power, which is growing in significance."

"While our research specializes in creating drug products to combat the health problems of the aged, we realize that such problems are not confined to a narrowly defined age group. The aging body represents a number of physical units, and several organs or systems of the body may become involved in the aging process. Since our metabolic processes frequently begin to slow down at the age of 35, we are formulating our products to affect the whole bodily system."

You can eat bread, lose weight, and be happy in the process. Evidence has been provided by twelve overweight women students at the University of Nebraska, whose slimming stint was described by Ruth M. Leverton, Professor of Human Nutrition at Nebraska, at this afternoon's session of the American Dietetic Association's Annual Meeting.

"The idea that bread is "fattening" and therefore should be avoided when planning a low-caloric diet is erroneous. Omitting bread in a reducing diet is unnecesary and leads to increased cost of the diet," Miss Leverton stated.

This conclusion was reached through the project which was conducted to study the needs of the body during weight reduction and to demonstrate the sensible place of bread in the diet.

For eight weeks the students were given a 1200 calorie diet which was nutritionally adequate in every respect except calories, and which included a slice of bread with butter at every meal. The daily menu offered a variety of foods and regularly included meat, milk, fruits, vegetables and bread.

In general, thick gravies and sauces, concentrated sweets, and calorie-packed desserts were omitted. At the end of eight weeks the twelve girls had lost a total of 227 pounds. They remained in excellent health and high morale.

Studies of food utilization by the usual scientific methods indicated that the girls were making good use of the proteins and minerals, which were supplied in generous amounts. However, they would have gone nutritionally bankrupt if their diet had not been kept at a nutritionally generous level.

ELIXIR ALURATE VERDUM 'ROCHE'

Elixir Alurate 'Roche' is now available in two forms: The established cherry-red form and a new, emerald-green form available under the name Elixir Alurate *Verdum* 'Roche.' The pleasing green color of Elixir Alurate Verdum enables the physician to provide a highly effective, well-tolerated sedative-hypnotic for those patients who suspect "pink medicine." Both Elixir Alurate and Elixir Alurate Verdum are distinguished by prompt action, rapid elimination, clear-headed awakening and relative freedom from "hangover" and cumulative effects. Both Elixir Alurate and Elixir Alurate Verdum are available in 6-ounce and 1-pint bottles.

MEDICAL LIBRARIANS MEET

The Upjohn library staff was host to the Midwest Regional Group of the Medical Library Association on Saturday, October 7th. The all-day session included visits to The Upjohn Company's library and both the Medical and Nursing School libraries at Borgess Hospital. Sixty-seven people were registered. Miss Alberta Brown, Upjohn Librarian and chairman of the Midwest Group, was in charge of the meeting.

The Medical Library Association was organized about fifty years ago for the purpose of fostering medical and allied scientific libraries and for the exchange of medical literature among its members. It includes libraries from schools of medicine, pharmacy, dentistry and nursing, as well as pharmaceutical companies. The Midwest Group, which was organized in January of this year, includes representatives from the states of Illinois, Minnesota, Iowa, Indiana, Michigan and Ohio, libraries such as those of the Mayo Clinic, the American Medical Association, The American College of Surgeons, University of Michigan Medical School, and the large midwestern pharmaceutical companies.

COMMERCIAL SOLVENTS AWARD ESTABLISHED FOR RESEARCH IN ANTIBIOTICS

The Commercial Solvents Corporation and the Society of American Bacteriologists announce the establishment of an annual award for outstanding research in the field of antibiotics.

The award, one thousand dollars and a gold medal, will be given to an individual or a group of individuals working in the Western Hemisphere who contribute to the better understanding of antibiotics. In selecting the winner of the award, particular attention will be given to the basic nature of the research upon which the award is made and its contribution to fundamental knowledge about antibiotics.

The Commercial Solvents Award will be administered by the Society of American Bacteriologists, and the recipient will be selected by a committee appointed by the President of the Society. It is expected that the first award will be presented at the annual meeting of the Society of American Bacteriologists in Chicago in May, 1951.

MAJORITY OF ARTHRITIC PATIENTS BENEFITED BY VITAMIN-HORMONE INJECTIONS

The great majority of patients with chronic forms of arthritis are improved strikingly by combined injections of Percorten, a hormone of the adrenal glands, and vitamin C, it was reported here today.

This finding was announced in the latest Bulletin of the Staff Conference of the DeCourcy Clinic, Cincinnati, Ohio, and confirms earlier reports from clinics here and abroad. More than one hundred patients with chronic arthritis of different types were treated at the DeCourcy Clinic in recent months—the most extensive study to date of the new method. In the new therapy, the intramuscular injection of 5 milligrams of Percorten (desoxycorticosterone acetate) is followed within 5 minutes by administration of one gram of vitamin C by vein.

"Our findings have convinced us," the DeCourcy Clinic physicians state, "that many patients with rheumatoid arthritis, especially in an acute phase, are decidedly benefited by combined injections of Percorten and Vitamin C. Palliative benefit also is obtained in a certain (considerable) percentage of cases of degenerative joint disease (osteoarthritis) similarly treated. The favorable responses obtained make possible or render more effective the application of physiotherapeutic and orthopedic measures."

Of 40 patients with rheumatoid arthritis, the Bulletin reports, 87.5 per cent (35 patients) manifested some improvement, ranging from slight to dramatic. Of 57 patients with osteoarthritis (degenerative joint disease), 80.7 per cent. (46 patients) showed a favorable response to the hormone-vitamin therapy.

The DeCourcy Clinic staff has concluded that "the hormone-vitamin treatment would seem to have a definite place in the therapeutic armamentarium." While impressively beneficial in a considerable percentage of patients, the new therapy "must be regarded as symptomatic and palliative in most patients and should be supplemented by physiotherapy and orthopedic measures."

NEW PRODUCT MICROPELLETS ORETON-F

(aqueous suspension of testosterone)

Manufacturer: Schering Corporation, Bloomfield, New Jersey.

Active Constituent: Pure crystalline Micropellets of testosterone, in aqueous suspension.

Action: Rapidly absorbed from the saline solution, resulting in es-

tablishment of a depot of testosterone in the tissues. Absorption begins promptly and continues for a long period.

Indications: MICROPELLETS ORETON-F is indicated in androgen deficiencies of the male, such as: hypogonadism (eunuchoidism), impotence, when due to failing testicular function, and the climacteric. It is also indicated, experimentally, in cirrhosis of the liver, cryptorchidism, dwarfism, involutional melancholia, and pruritus (senile). Female uses for MICROPELLETS ORETON-F include: advanced breast carcinoma, functional uterine bleeding, menopausal syndrome with metrorrhagia, dysmenorrhea, inhibition of lactation, and postpartum after-pains. Among experimental indications for females are endometriosis and frigidity; for both sexes, angina pectoris, Addison's Disease (supplemental to therapy with *Cortate*, enuresis, osteoporosis, premature infants, and uremic states.

Dosage: In males: MICROPELLETS ORETON-F 25 mg. three to five times weekly in the male climacteric; three to four times weekly in impotence, with reductions of dosage in each case to maintenance levels.

In females: MICROPELLETS ORETON-F 100 mg. three times weekly as initial therapy in advanced breast carcinoma; functional uterine bleeding, 25 mg. every other day for three or four doses; dysmenorrhea, 10 mg. daily for the last 10 days of cycle; inhibition of lactation, 25 mg. twice daily for two days; postpartum after-pains, 25 mg. after delivery and repeated 8 hours later, if desired.

Administration: MICROPELLETS ORETON-F is administered by intramuscular injection. A 21-gauge, one and one-half inch needle is recommended. After withdrawal of needle, brief massage over the injection site serves to distribute and aid absorption of the hormone.

Packaging: Multiple dose vials of 10 cc., containing 25 mg. or 50 mg. per cc. Boxes of 1 and 6 vials.

NEW VITAMIN FORMULA FOR PREGNANCY OFFERED

A new highly potent vitamin and mineral formula in capsule form, called Calirad Super, is now being offered by Winthrop-Stearns, Inc., pharmaceutical manufacturers. Indicated primarily for use in pregnancy, Calirad Super is also valuable for correcting other nutritional deficiencies.

The formula per capsule is as follows:

Vitamin A 1,500 USP units
Vitamin D (Viosterol) 300 USP units
Vitamin B_1 1 mg.
Vitamin B_2 1 mg.
Vitamin C 30 mg.
Niacinamide 8 mg.
Potassium Iodide 0.1 mg.
DiCalcium Phosphate, Anhyd. 568 mg.
Ferrous Gluconate NF 50 mg.
Menadione USP 0.15 mg.

INSULIN REDUCES COST OF CORTISONE THERAPY IN ARTHRITIS

What may prove to be a revolutionary development in the treatment of rheumatoid arthritis was disclosed in a preliminary report by Doctors Edward Henderson, John W. Gray, Marvin Weinberg, Evelyn Z. Merrick and Harry Seneca, published in the current issue of the Journal of Clinical Endocrinology.

These scientists discovered that when insulin, the hormone used in diabetes, is given simultaneously with cortisone, very much smaller doses of cortisone than heretofore used may be effective. This combination was reported to produce the same degree of relief in arthritis as when cortisone is used alone in the customary large doses.

Cortisone is the adrenal compound reported by Doctors Hench and Kendall of the Mayo Clinic a little more than a year ago as producing spectacular improvement in rheumatoid arthritis. Its use in medicine has been handicapped, the scientists, explained, by it potential dangers and the extremely high cost of treatment.

The principle of using insulin together with cortisone was developed by Doctor Henderson, Director of the Clinical Research Division of Schering Corporation, Bloomfield, New Jersey, and by Doctor Marvin Weinberg, his associate, on the basis of animal and laboratory experiments conducted at the College of Physicians and Surgeons of Columbia University by a third member of the Schering team, Doctor Harry Seneca.

Through the cooperation of Doctor George C. Schicks, Director of St. Barnabas Hospital, Newark, N. J., and with Doctor John W. Gray, distinguished rheumatologist and Director of the Arthritis Clinic at St. Barnabas, and his associate, Doctor Merrick, special arrangements for carrying out the clinical studies, additional trained staff members including special nurses, and all other essentials of an advanced research program were worked out.

Intense interest has focused on the cortisone treatment of arthritis for over a year since it was first announced at the Mayo Clinic, but physicians have been handicapped by the limited supply of the drug, its prohibitively high cost, and certain unfortunate side effects which develop incidental to the treatment, when large doses of cortisone are used. Many efforts have been made to produce the drug in larger quantities and at lower cost, but prior to the St. Barnabas research nothing had been done to make smaller quantities of the drug serve the purpose. The research workers have stated that the new method does not merely cut the cost of treatment to one-half or less, but also offers a means of avoiding some of the dangerous actions of the drug, very familiar to physicians who have had experience with cortisone. In addition, it is said, the new method is the first of many improvements, still to come, which may bring the cost of treatment finally within reach of the majority of arthritis sufferers.

Twelve patients with typical rheumatoid arthritis were hospitalized in the St. Barnabas Hospital for this study which was supported entirely by a grant provided by the officers of Schering Corporation. Some were early cases and some were chronic cases of 20 years standing with far advanced arthritis. On doses of only 25 mg. cortisone daily (the usual dose is 100 mg. daily), most of the patients showed a prompt drop in the sedimentation rate of the blood which is considered by rheumatologists to be an indication of the activity of the disease. The patients also showed some evidence of clinical improvement. When advanced to 50 mg. per day, which is half the usual dose, all patients

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By developing an entirely new type of enzymatic carrier, literally "a tablet within a tablet," Robins now makes available a triple-enzyme digestant—Entozyme. In *one small specially constructed tablet*, Entozyme "packs" pepsin, pancreatin and bile salts—in such a way that they are released only at the gastro-intestinal level of optimal activity. Thus Entozyme greatly simplifies and makes more effective the treatment of complex digestive disturbances of the gastro-intestinal tract. Clinical studies[1,2,3] have demonstrated the value of Entozyme in such conditions as chronic cholecystitis, chronic duodenal ulcer, acute and chronic pancreatitis and certain postoperative syndromes of the gastro-intestinal tract—in relieving nausea, belching, distention, anorexia, food intolerance, etc.

FORMULA: Each specially constructed tablet contains Pancreatin, U.S.P., 300 mg.; Pepsin, N.F., 250 mg.; Bile Salts, 150 mg.

DOSAGE: One or two tablets after each meal, or as directed by physician, without crushing or chewing.

AVAILABLE: Bottles of 25 and 100.

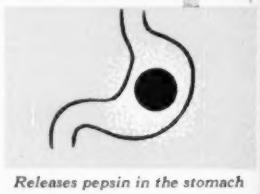
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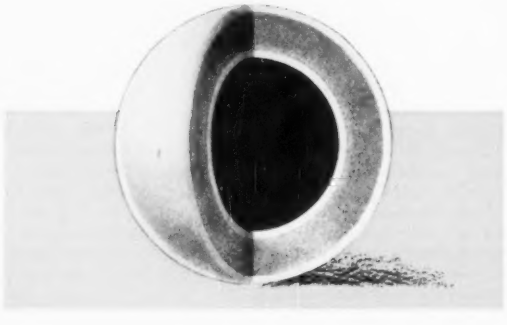
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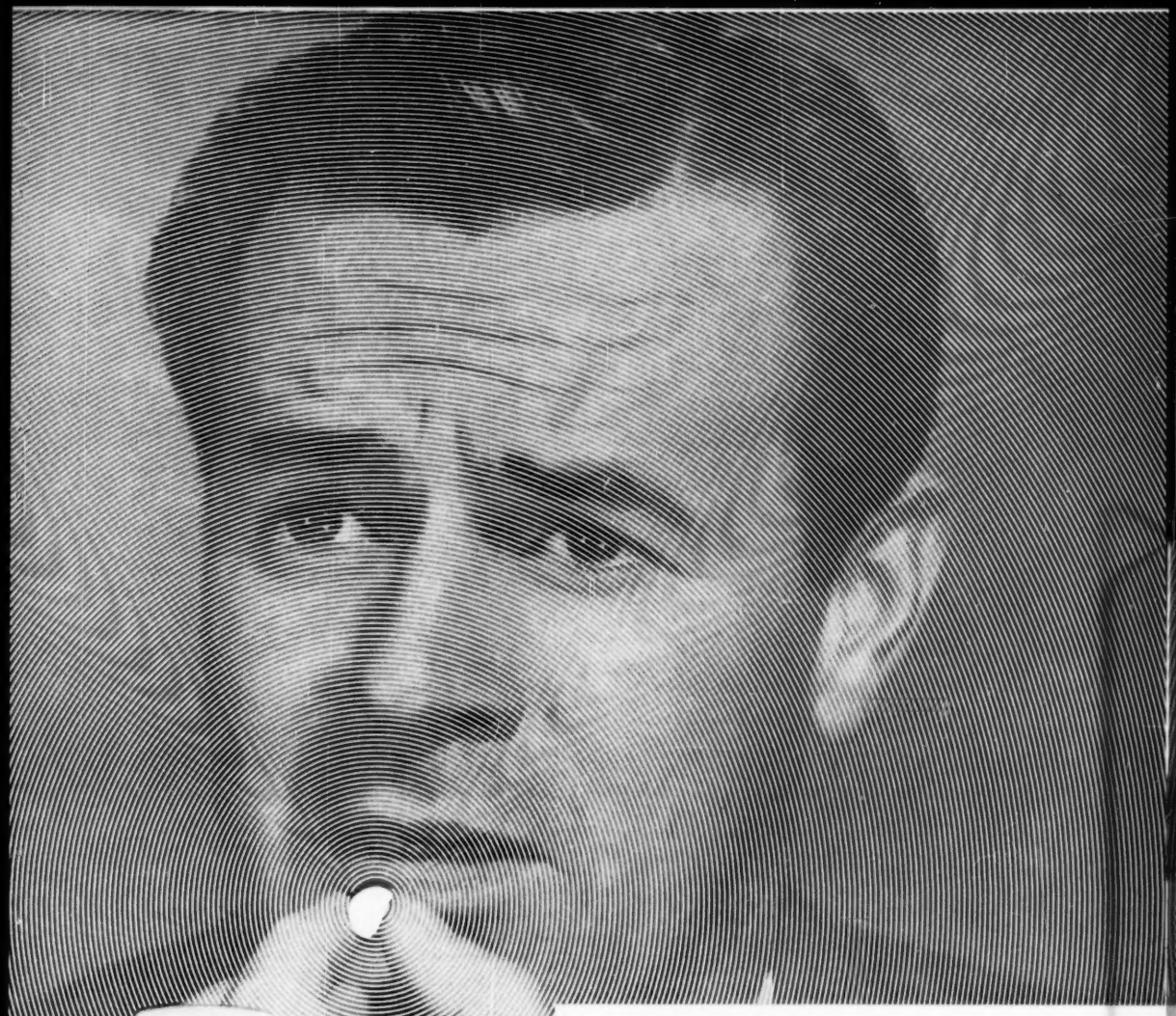
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showed subjective improvement, relief of pain, and 10 to 12 patients showed objective evidence of improvement by normal sedimentation rates, increased movement of joints, and diminution of swelling.

These researchers emphasize with the usual scientific caution that this is a preliminary report and that many more carefully controlled hospital studies are necessary before any definite conclusions can be reached.

CORTONE

MERCK & CO., Inc. announces that CORTONE (the Merck brand of cortisone) will be made generally available on or about November 1 through distributors, hospitals, institutions, and pharmacies for use by the physician in his daily practice. Meanwhile, physicians may continue to obtain CORTONE from hospitals, and patients need not be hospitalized except at the physician's discretion.

A further price reduction is announced by the company effective immediately. The suggested list price to physicians is $35 a gram. The price charged to hospitals during the past few months has been $50 a gram. The company has succeeded in reducing the price of CORTONE to less than one-fifth of that charged to investigators a little over a year ago. These savings have been accomplished through research and process improvements.

In rheumatoid arthritis, where prolonged treatment with CORTONE is usually required, clinical investigators now indicate that almost all patients can be maintained on one-tenth of a gram a day. Some patients can be maintained on as little as one-twentieth of a gram a day.

Since July 1950 CORTONE has been available on a limited basis, and distribution has been through hospitals only.

AMES ANNOUNCES NEW TEST FOR ALBUMINURIA

Sulfosalicylic acid has long been recognized as one of the most dependable tests for albuminuria. The Ames Company, Inc., Elkhart, Indiana, has announced that after three years of research they have developed a stable, reagent tablet containing sulfosalicylic acid now being marketed under the name BUMINTEST (Brand) Reagent Tablets.

The advantages of this splendid test are the uniformity of composition, the elimination of heat, speed in running a test and ease of interpretation. As a safety feature the tablets are noncaustic and noncorrosive.

Ames intends to promote BUMINTEST as a companion product to its diagnostic reagent tablets, CLINITEST, ACETEST and HEMATEST. The theme will be that with these four reagent tablets an accurate inexpensive diagnosis of urine can be performed by the doctor or laboratory in a matter of a few minutes.

BUMINTEST (Brand) Reagent Tablets are now available through regular drug channels in bottles of 32, 100 and 500.

LITRISON CAPSULES 'ROCHE'

A new, liver-protecting dietary supplement, LITRISON 'Roche' provides—in an easy-to-swallow capsule—twelve nutritional factors of importance in the management of liver diseases. LITRISON is valuable whenever there is reparable damage or functional impairment of the liver responsive to lipotropic factors and fat and water-soluble vitamins. The formula of LITRISON is based on recent findings which show the synergistic action of lipotropic agents, vitmain B_{12}, folic acid, vitamins A and D, and B-complex factors in the prevention and treatment of liver diseases. A daily dose of six LITRISON capsules is recommended.

NOTICE

E. Claiborne Robins, president of the A. H. Robins Company, Inc. of Richmond, Va. has been elected to the Board of Trustees of the projected Richmond Memorial General Hospital for which a $5,000,000 fund-raising campaign is in progress. Some three months ago a contribution of $30,000 was made by the A. H. Robins Co. and the Robins family, for the establishment of a pharmacy in the hospital to memorialize Mr. Robins' father who died in 1912, the latter was the firm's first president until his death.

NEW CURARE-LIKE DRUG OFFERS AID TO SURGEONS

Pharmacological experiments with a new curare-like drug give promise of providing an improved tool to surgeons performing major operations, Dr. James O. Hoppe of the Sterling-Winthrop Research Institute revealed in a paper prepared for presentation before the Congress of Anesthetists, meeting with the International Anesthesia Research Society. Sessions are at the Roney Plaza Hotel, Miami Beach, Fla.

Major surgery requires relaxation of the voluntary muscles, now achieved by the use of d-tubocurarine chloride, an alkaloid obtained from curare, the ancient South American arrow-poison. Prior to the advent of d-tubocurarine it was necessary to resort to the use of large amounts of anesthetic in order to obtain adequate muscular relaxation but frequently this reacted unfavorably on the blood pressure and respiration.

Dr. Hoppe reported on a synthetic developed by Dr. Chester J. Cavallito of the Institute. He described it chemically as 2,5-bis-(3 diethylaminopropylamino) -benzoquinine-bisbenzylchloride or WIN 2747. Clinical experiments are proceeding with the compound directed by Winthrop-Stearns Inc.

Comparing WIN 2747 with d-tubocurarine, Dr. Hoppe found it to have curare-like activity in several species of laboratory animals ranging from one half to five times as great. Necessary relaxation of the voluntary or skeletal muscles was obtained with smaller amounts of the new compound, reducing many objectional effects of deep anesthesia.

Dr. Hoppe also found that WIN 2747 does not cause any appreciable fall in blood pressure, whereas d-tubocurarine chloride does. It also appears to have little or no effect on the heart.

The experiments reported represent a new chapter in a long romantic history involving curare. This drug brewed from a wild South American vine, was first used more than 300 years ago by native Indians as a poison with which to tip their war or hunting arrows. It had a rapid paralyzing effect on its victims.

About 100 years ago, the French scientist, Claude Bernard discovered the properties of curare which cause relaxation of the voluntary muscles.

AMER. JOUR. DIG. DIS.

NEW- Chlorophyll therapy for peptic ulcers!

CHLORESIUM POWDER

EFFECTIVE- in a recently reported clinical series*, *complete healing was obtained in 58 out of 79 cases of long-standing peptic ulcers within 2 to 7 weeks*—with new chlorophyll powder!

No special diets were required. No restrictions on smoking, alcoholic beverages or daily activity. Three out of four cases got complete symptomatic relief within one to three days!

Incorporating the same water-soluble chlorophyll derivatives well known to the medical profession in Chloresium Ointment and Chloresium Solution (Plain), Chloresium Powder is a completely nontoxic combination product specifically designed to allow prolonged contact of tissue-stimulating chlorophyll with the ulcer crater. At the same time, it provides the essential buffering and protective action found in the usual ulcer medication.

The "Bonus" Action of Chloresium Powder

1. **Prolonged protective coating** (dehydrated powdered okra).
2. **Prompt antacid action** (alum. hydroxide, magnesium trisilicate)—no alkalosis, no acid rebound, no interference with bowel regularity.

PLUS

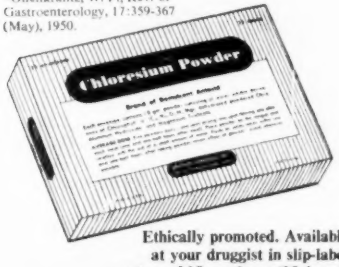
3. **Promotion of granulation tissue** (with tissue-stimulating chlorophyll). *Only Chloresium Powder gives this tissue-stimulating "bonus!"*

Chloresium Powder, in this clinical trial, demonstrated its effectiveness to the peptic ulcer patient quickly in the form of complete symptomatic relief. It demonstrated its effectiveness to the physician, under roentgenological examination, in prompt healing of the ulcer crater—usually in 2 to 7 weeks—even in cases which had been resistant to other therapy. (The minimum known history of the ulcers treated was two years.)

The freedom from dietary and other restrictions which Chloresium Powder allows has obvious patient appeal and can greatly simplify the task of insuring patient cooperation.

We invite you to try Chloresium Powder on your most resistant case. Just mail the coupon below for a five-day trial supply.

*Offenkrantz, W. F., Rev. of Gastroenterology, 17:359-367 (May), 1950.



Ethically promoted. Available at your druggist in slip-label cartons of 25 envelopes (25 doses).

Chloresium® Powder

Natural nontoxic chlorophyll therapy for the treatment of peptic ulcers

FREE—CLINICAL SAMPLE

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Please send full-size sample of Chloresium Powder and reprint of the clinician's paper on chlorophyll therapy for peptic ulcers.

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By definition

clinically, ***hydrocholeresis*** might well be defined as "the therapeutic effect produced by *Decholin Sodium* (brand of sodium dehydrocholate)," so specifically is this pure bile acid derivative identified with the basic experimental and clinical studies on medical management in biliary tract disorders.

pharmacologically, ***hydrocholeresis*** means increased total output of bile with low specific gravity, low viscosity and low content of solids. This is in contrast to *choleresis*, a slightly increased flow of bile with high viscosity. In sum, *hydrocholeresis* means *more and thinner bile*, as required for stimulation and non-surgical drainage of the biliary tract. *Decholin Sodium* is the most effective hydrocholeretic agent available to medicine.

Decholin Sodium

practically, ***hydrocholeresis*** is produced with safety and economy of dosage by administering *Decholin Sodium* alone. For conditions requiring prolonged treatment, *Decholin Sodium* administrations may be supplemented or combined with *Decholin* tablets, orally.

Decholin Sodium

(brand of sodium dehydrocholate)

20% solution for intravenous administration:
3 cc. and 10 cc. ampuls: boxes of 3 and 20.
5 cc. ampuls: boxes of 3, 20 and 100.

Decholin Tablets of 3¾ grains (0.25 Gm.), in bottles of 25, 100, 500, 1000 and 5000.

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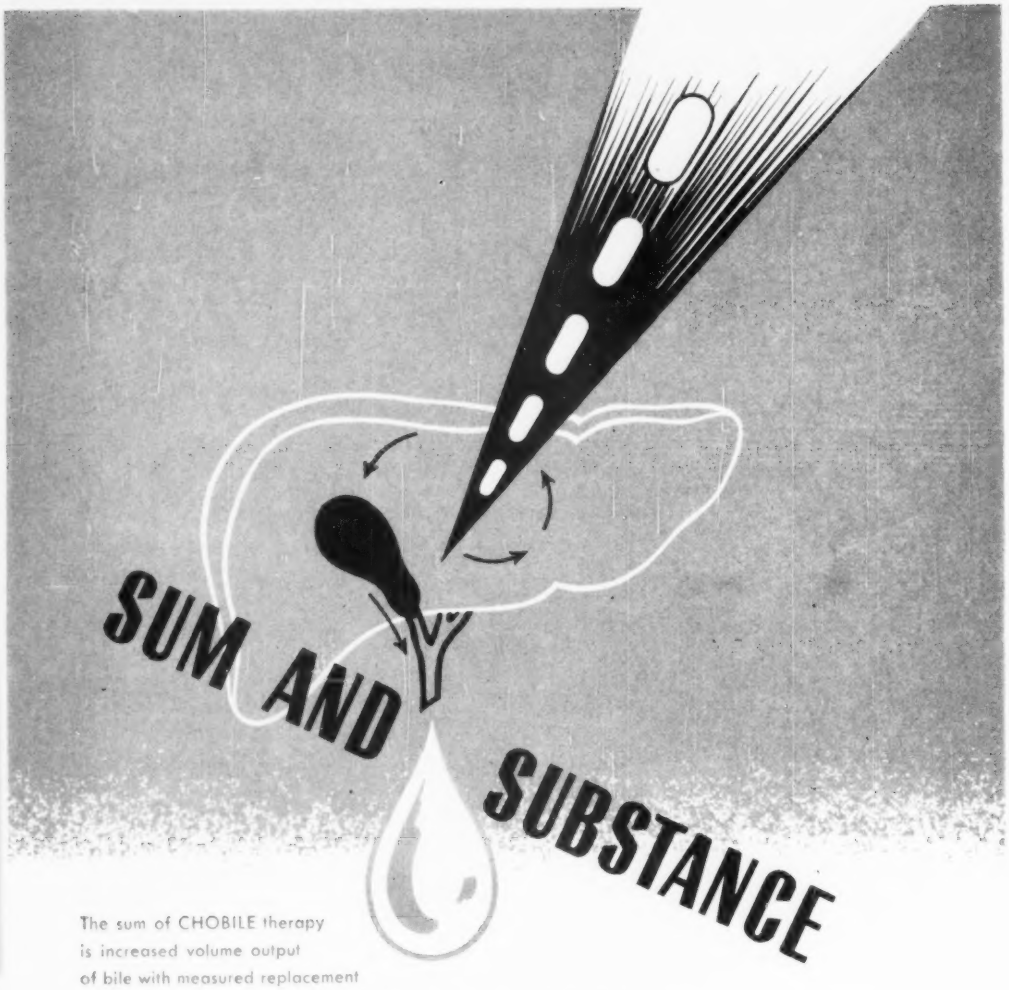
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Each Dayamin Capsule contains:

Vitamin A	10,000 U.S.P. units
Vitamin D	1000 U.S.P. units
Thiamine Hydrochloride	5 mg.
Riboflavin	5 mg.
Nicotinamide	25 mg.
Pyridoxine Hydrochloride	1.5 mg.
Pantothenic Acid (as calcium pantothenate)	5 mg.
Ascorbic Acid	100 mg.



The sum of CHOBILE therapy is increased volume output of bile with measured replacement of indispensable cholic acid, the substance credited with being the crucial factor in bile acid formation.

Thus, CHOBILE produces a biliary flush without the risk of secretory exhaustion . . . by supplying cholic acid for maintaining the concentration of natural bile acids.

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Samples and literature on request.

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PRESCRIBED FOR MORE THAN 7 YEARS

IRWIN, NEISLER & CO. DECATUR, ILL.

Bananas... a natural sweetener

● One medium-sized fully ripe banana (yellow peel flecked with brown) contains the equivalent of 4 to 5 level teaspoons natural sugar as follows:

Sugars in the Banana Total 20.4%
4.6% dextrose
3.6% levulose
12.2% sucrose

VITAMIN CONTENT PER 100 GRAMS

A . . . . . 250-335 International Units
B_1 (Thiamine) . . . . . 42-54 Micrograms
B_2 or G (Riboflavin) . . . . 88 Micrograms
Niacin (Nicotinic Acid) . . . .6 Milligrams
C (Ascorbic Acid) . . . . . 10-11 Milligrams

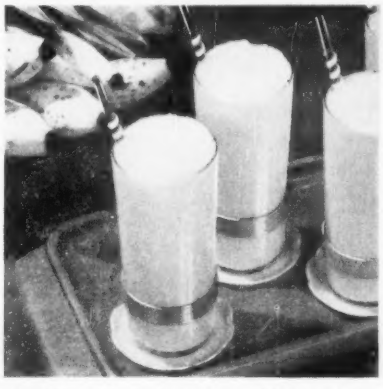
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IN MILK SHAKES — For high caloric and high vitamin diets

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"DIETARY USES OF THE BANANA IN HEALTH & DISEASE,"
by L. Jean Bogert.

* * *

Educational Department 3
UNITED FRUIT COMPANY
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Banana Milk Shake

1 fully ripe banana* **1 cup (8 ounces) COLD milk**

**Use fully ripe banana . . . peel well flecked with brown*

Peel banana. Slice into a bowl and beat with electric mixer or rotary egg beater until smooth and creamy. Add milk and mix thoroughly. Serve immediately.

Makes 1 large or 2 medium-sized drinks.

Banana Milk Shake is only one of the many new uses for Bananas.



THE

velvety softness

THAT IS KIND TO THE BOWEL

In the treatment of constipation, Kondremul contributes a velvety soft colloidal emulsion of microscopically fine particles which mix intimately with the dry fecal residue—easing elimination and encouraging regular bowel habits.

To meet various types of constipation, Kondremul is supplied in three forms:

KONDREMUL Plain (containing 55% mineral oil)

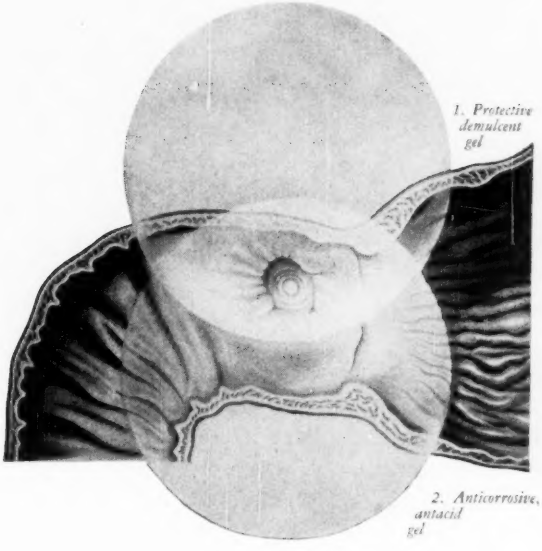
KONDREMUL with non-bitter Extract of Cascara (4.42 Gm. per 100 cc.)

KONDREMUL with Phenolphthalein—.13 Gm.(2.2 grs.) phenolphthalein per tablespoonful

KONDREMUL

...an emulsion of Mineral Oil and Irish Moss

THE E. L. PATCH COMPANY
STONEHAM, MASS.



double action for outstanding benefit ***...in Peptic Ulcer***

Amphojel is a colloidal mixture of two essentially different types of alumina gel.

The *demulcent gel*, like a "mineral mucin," provides local protection.

The *antacid gel* instantly stops gastric corrosion and relieves pain.

Together, they provide a favorable environment for the healing of the ulcer.

No alkalosis or acid rebound, because

Amphojel®

ALUMINUM HYDROXIDE GEL, Wyeth

does not disturb the normal acid-base equilibrium of the blood stream.
Bottles of 12 fl. oz. at all pharmacies.
Also, handy tablets of 5 gr.: boxes of 30, bottles of 100; and 10 gr.: boxes of 60.

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Wyeth Incorporated, Philadelphia 3, Pa.

It has only been in the last 15 years, however, that medical use has been safely made of this development, because of its extreme toxicity. In 1935, British scientists uncovered the chemical structure of the plant drug, and the follow-through resulted in the development of d-tubocurarine chloride.

For 80 years numerous attempts have been made to synthesize a drug which would serve medicine as effectively or more so than curare. Most recent advances came in 1946 from the laboratories of Bovet and Associates in Italy. Then two groups of investigators in England, Barlow and Ing and Paton and Zaimes prepared a synthetic compound with activities approaching curare. Now in this country, Dr. Cavallito at the Sterling-Winthrop Research Institute has synthesized an entirely new curare-like compound which appears to be at least as active and without the undesirable side effects of the expensive d-tubocurarine.

will reduction of serum cholesterol extend life?

by preventing atherosclerosis

"It is generally accepted that persistently high plasma cholesterol levels are associated with development of arteriosclerosis,"[1] a major cause of coronary thrombosis fatalities[2] and a "burning problem" in diabetes.[3]

Accumulating evidence shows that lipotropic therapy will reduce elevated blood cholesterol levels[4-5] ... and even may "prevent or mitigate" cholesterol depositions in the intima of blood vessels in man and animals.

It has been reported[6] that in patients who have survived acute coronary occlusion, lipotropic therapy may significantly prolong life as compared to similar untreated groups.

now contains added lipotropic vitamin B_{12}

methischol capsules syrup

for complete lipotropic therapy

suggested daily therapeutic dose of 9 capsules or 3 tablespoonfuls provides	
Choline Dihydrogen Citrate	2.5 Gm.*
dl-Methionine	1.0 Gm.
Inositol	0.75 Gm.
Vitamin B_{12}	9 mcg.
Liver fractions from 36 Gm. liver	

*present in Methischol Syrup as 1.15 Gm. choline chloride



400% more cholesterol in coronary arteries in fatal thrombosis

"The average cholesterol content of the coronary arteries in a group of patients who died from acute coronary artery thrombosis was four times as great as the average cholesterol content of the coronary arteries in a comparable group of control patients."[7]

Write for samples and literature

1. J.A.M.A. 135:836, 1947.
2. Morrison, L. M. and Tabenson, S. D.: Amer. Heart J. 33:42, 1947.
3. Joslin, E. P.: Proc. Conference, 17:343, 1946.
4. Hechtman, S. B.: Exp. Med. & Surg., 1:45, May-Apr. 1943.
5. Entenman, J. and Moore, D. H.: Amer. Heart J. 25:2, Sept. 1943.
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8. Morrison, L. and Levine, S. Z.: Amer. Heart J. 28:43, Sept. 1944.

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AMES COMPANY

With competition in the pharmaceutical industry increasing more and more each year, the importance of the well-trained detail man is becoming increasingly evident.

In an address before the annual sales convention of the Ames Company, Mr. William T. Doyle, President of the Research Society, stated that continuing marketing research studies carried on by his organization shows the detail man to be an over-growing factor in the competition to introduce new products successfully, and to keep the old ones sold as well.

Mr. Doyle pointed out that his company's Prescription Audit Reports reveal that the antibiotics and antihistaminics alone account for close to 20 per cent of prescription being written. Since these two types of therapy are less than ten years old it is quite apparent how important new product development is to a company and also why it is so necessary to have a staff of well trained detail men to influence the doctors to prescribe them.

Also of interest was a recent study completed by the Research Society which showed that over a five day period physicians were being exposed, through detailing and direct mail, to a high of 83 trade names and a low of 61. Mr. Doyle stressed that the new language of trade names which is being built up necessitates continuous detail support, backed up by medical journal advertising, direct mail and a strong educational program with the pharmacist who after all is the link between doctor, manufacturer and patient.

MEDICINE HAILED AS POTENT MEDIUM FOR WORLD PEACE

New York—October—"World medicine is one of the most potent universal mediums of promoting international good will and peace," Dr. Elwood A. Sharp, director of the Department of Clinical Investigation of Parke, Davis & Co., told medical scientists from 38 countries at a dinner given to them by the company at Hotel Roosevelt here.

Greeting delegates, alternates, observers and their wives attending the fourth general assembly of the

quick relief and healing

in peptic ulcer...

Resinat, pepsin inactivator and antacid, brings quick relief of pain and speeds healing of peptic ulcer.

Weiss, S., et al.,[1] used Resinat in the treatment of 120 ulcer patients. These investigators report "symptomatic relief occurred within 48-72 hours and x-ray follow-up showed regression of ulcer crater in two to four weeks."

Resinat is insoluble, chemically and physiologically inert. It does not remove chlorides, phosphates, vitamins or minerals from the body. It does not alkalinize the system or cause acid rebound.

Resinat inactivates pepsin and neutralizes excess gastric acidity.

Available in Capsules, 0.25 Gm. – Tablets, 0.5 Gm. – Powder, 1 Gm. Packets.

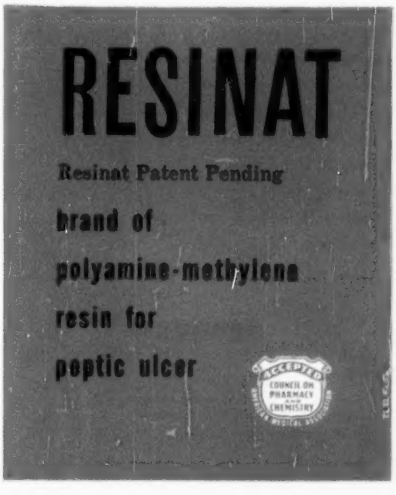
1. Weiss, S., et al.: Rev. Gastroenterology 16:501-509 (June) 1949.

Literature and samples available.

More than Half a Century of Service to the Medical Profession

The National Drug Company

Philadelphia 44, Pa.



World Medical Association on behalf of Dr. A. W. Lescohier, President of Parke, Davis & Co., Dr. Sharp pointed out how world medicine knows no national boundaries in its efforts to cure and prevent the ills of mankind.

Austria and Bulgaria were the only nations represented that are close to the Soviet and its satellite countries.

"We in the Americas" continued Dr. Sharp, in an informal greeting to the 300 diners, "believe The World Medical Association, and the 38 national organizations of which it is composed, is a medium which will give us an opportunity to learn from our medical brethren in other countries much that we can use, and that we in turn will contribute to their medical science.

"At the risk of being trite, I would like to remind our guests, that *medicine* is the only member of the professions, arts, or crafts, that exerts unusual efforts to deny itself the economic privilege that accrues to its profession through its efforts to prevent and eradicate diseases."

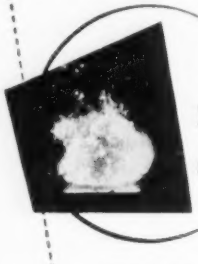
Reminding his hearers that the pharmaceutical industry was worldwide—Parke, Davis & Co., for example, has research laboratories on every continent including the latest one opened in London in 1950, with branch offices and well-trained personnel throughout the world—and constantly cooperating in the integration of research and the practice of medicine, Dr. Sharp said.

"There are so many unsolved medical problems, such as tuberculosis and cancer, that all of us must continue to strive to our utmost to solve present problems. Every time we solve one problem we are able to free a corps of scientists to attack another problem. Therefore, world medicine advances to the universal benefit of mankind. Cancer and tuberculosis alone will require major efforts of all, and the greatest minds in world medicine to be solved effectively.

Assisting Dr. Sharp were: W. Richard Jeeves, sales manager of the foreign sales department, and Dr. Eugene H. Payne, member of the Department of Clinical Investigation of Parke, Davis & Co.

INDEX TO ADVERTISERS

Abbott Laboratories XVII
Ames Co., Inc. XVI
Ayerst, McKenna & Harrison VIII
Bio-Ramo Drug Co., Inc. II
Ciba Pharmaceutical Products I
The Fruit Dispatch Co. XIX
Hoffmann-La Roche, Inc. XXIV
Irwin, Neisler & Co. XVIII
Eli Lilly and Copany VIII
The S. E. Massengill Co. VI
The National Drug Co. XXIII
The E. L. Patch Co. XX
Chas. Pfizer & Co., Inc. 3rd Cover
A. H. Robins Co., Inc. .... IV and V
A. H. Robins Co., Inc. XII & XIII
The Rystan Co. XV
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One teaspoonful (5 cc.) provides

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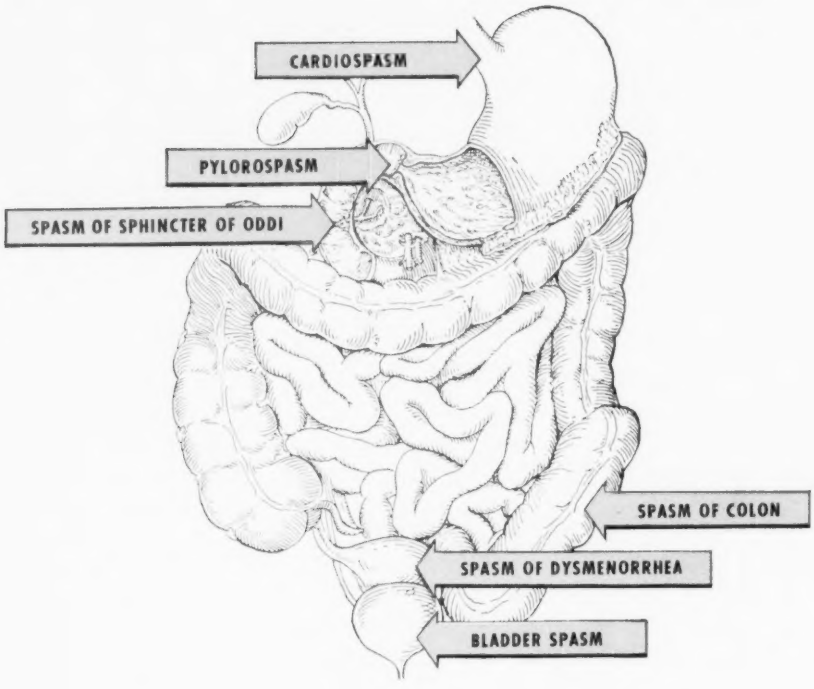
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High dosage concentration assures therapeutic efficacy without requiring new and unwieldy dosage schedules.

Available at prescription pharmacies in bottles containing 1 fl. oz.

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PAVATRINE® WITH PHENOBARBITAL

exerts two types of spasmolysis—neurotropic and musculotropic—in addition to providing central nervous system sedation. Pavatrine with Phenobarbital is non-narcotic and effective on oral administration. G. D. Searle & Co., Chicago 80, Illinois.

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